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L6 ANSWER 1 OF 15 USPATFULL
AN 2000:74115 USPATFULL
TI Polynucleotides encoding human CTLA-8 related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States
Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S.
corporation)
PI US 6074849 20000613
AI US 1996-685239 19960718 (8)

RII Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
DT Utility
EXNAM Primary Examiner: Draper, Garnette D.
LREP Brown, Scott A.; Sprunger, Suzanne A.; DesRosier, Thomas J.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1658

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotides encoding human CTLA-8 related proteins are disclosed.
Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L6 ANSWER 2 OF 15 USPATFULL

AN 2000:37900 USPATFULL

TI Human CTLA-8 and uses of CTLA-8-related proteins

IN Jacobs, Kenneth, Newton, MA, United States

Kelleher, Kerry, Marlborough, MA, United States

Carlin, McKeough, Cambridge, MA, United States

Goldman, Samuel, Acton, MA, United States

Pittman, Debra, Windham, NH, United States

Mi, Sha, Belmont, MA, United States

Neben, Steven, Acton, MA, United States

Giannotti, Joanne, Acton, MA, United States

Golden-Fleet, Margaret M., Medford, MA, United States

PA Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)

PI US 6043344 20000328

AI US 1998-34810 19980304 (9)

RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now abandoned

which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19 Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995, now patented, Pat. No. US 5707829

PRAI US 1995-35347 19950719 (60)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Lahive & Cockfield, LLP; Mandragouras, Esq., Amy E.; Lauro, Esq., Peter C.

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN 10 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 1761

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotides encoding human CTLA-8 and related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L6 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2001 ACS

AN 1999:736789 CAPLUS

DN 132:48827

TI Autocrine regulation of IL-12 receptor expression is independent of secondary IFN- γ secretion and not restricted to T and

NK cells

AU Thibodeaux, Deborah K.; Hunter, Sharon E.; Waldburger, Kristine E.; Bliss,

Judy L.; Trepicchio, William L.; Sypek, Joseph P.; Dunussi-Joannopoulos, Kyriaki; Goldman, Samuel J.; Leonard, John P.

CS Preclinical Research and Development, Genetics Institute, Andover, MA, 01810, USA

SO J. Immunol. (1999), 163(10), 5257-5264

CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB

The biol. response to IL-12 is mediated through specific binding to a high affinity receptor complex composed of at least two subunits (designated IL-12R.beta.1 and IL-12R.beta.2) that are expressed on NK cells and activated T cells. The selective loss of IL-12R.beta.2 expression during Th2 T cell differentiation suggests that regulation of this receptor component may govern IL-12 responsiveness. In murine assays, down-regulation of IL-12R.beta.2 expression can be prevented by treatment with IFN-.gamma., indicating

that receptor expression and hence IL-12 responsiveness may be regulated, at least in part, by the local cytokine milieu. In this study, the authors report that cellular expression of both IL-12R.beta.1 and .beta.2 mRNA is increased in the lymph nodes of naive mice following systemic administration of murine rIL-12 (rmIL-12). Changes in IL-12R mRNA were assocd. with increased IFN-.gamma. secretion following ex vivo activation of lymph node cells with rmIL-12, indicating the presence of a functional receptor complex. Expression of IL-12R mRNA was not

restricted to lymph node T cells, and its autocrine regulation was independent of secondary IFN-.gamma. secretion. Data from fractionated lymph node cells as well as rmIL-12-treated B cell-deficient mice suggest that IL-12-responsive B cells may represent an alternative cellular source for IFN-.gamma. prodn. However, the strength of the biol.

response to rmIL-12 is not governed solely by receptor expression, as rmIL-12-induced IFN-.gamma. secretion from cultured lymph node cells is accessory cell dependent and can be partially blocked by inhibition of B7 costimulation.

RE.CNT 40

RE

- (1) Cella, M; J Exp Med 1996, V184, P747 CAPLUS
 - (2) Chan, S; J Exp Med 1991, V173, P869 CAPLUS
 - (3) Chizzonite, R; J Immunol 1992, V148, P3117 CAPLUS
 - (4) de Kruffy, R; J Immunol 1997, V158, P359 CAPLUS
 - (5) Desai, B; J Immunol 1992, V148, P3125 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 2000:59937 BIOSIS
DN PREV200000059937
TI Vaccines with interleukin-12-transduced acute myeloid leukemia cells elicit very potent therapeutic and long-lasting protective immunity.
AU Dunussi-Joannopoulos, Kyriaki (1); Runyon, Kathlene; Erickson, Jamie; Schaub, Robert G.; Hawley, Robert G.; Leonard, John P.
CS (1) Genetics Institute, 1 Burt Rd, Andover, MA USA
SO Blood, (Dec. 15, 1999) Vol. 94, No. 12, pp. 4263-4273.
ISSN: 0006-4971.
DT Article
LA English
SL English
AB Interleukin-12 (IL-12) is a heterodimeric cytokine mediating a dynamic interplay between T cells and antigen-presenting cells (APCs). Preclinical studies have demonstrated that recombinant murine IL-12 (rmIL-12) promotes specific antitumor immunity mediated by T cells in several types of tumors. However, the in vivo antitumor properties of IL-12 in acute myeloid leukemia (AML) have not been previously reported. We show here in a murine AML model that systemic administration of rmIL-12 significantly delays tumor growth but is incapable of rescuing mice from lethal leukemia. In

contrast, AML cells genetically modified to express IL-12 (IL12-AML) using murine stem cell virus (MSCV) p40 + p35 elicited very potent antileukemic activity. Vaccines with lethally irradiated IL12-AML cells protect naive mice against challenge with wild-type AML cells and, more importantly, can cure mice bearing a considerable

leukemic

burden. Immunized mice show no signs of systemic IL-12 toxicity and their spleen histology is comparable with naive mice spleen. In vivo depletion of IL-12, interferon-gamma (IFN-gamma), or CD8+ T cells after injections with live IL12-AML cells abrogates completely the antileukemia immune responses. Studies on the in vitro effects of IFN-gamma on AML cells demonstrate enhanced expression

of

major histocompatibility complex (MHC) and accessory molecules and induction of the costimulatory molecules B7.1 and B7.2, but no

significant

direct antiproliferative effect. 51Cr release assays show that rejection of live IL12-AML cells supports the development of long-lasting leukemia-specific cytotoxic T lymphocyte (CTL) activity. In conclusion, our results demonstrate that IL12-AML vaccination is a safe and potent immunotherapeutic approach that has a great potential to eliminate

minimal

residual disease in patients with AML.

L6 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2001 ACS

AN 2000:177320 CAPLUS

DN 133:191823

TI Dose and timing of interleukin (IL)-12 and timing and type of total-body irradiation: effects on graft-vs.-host disease inhibition and toxicity of exogenous IL-12 in murine bone marrow transplant recipients

AU Sykes, Megan; Pearson, Denise A.; Taylor, Patricia A.; Szot, Gregory L.; Goldman, Samuel J.; Blazar, Bruce R.

CS BMT Section, Transplantation Biology Research Center, Surgical Service, Massachusetts General Hospital/Harvard Medical School, Boston, MA, 02129, USA

SO Biol. Blood Marrow Transplant. (1999), 5(5), 277-284
CODEN: BBMTF6; ISSN: 1083-8791

PB Carden Jennings Publishing

DT Journal

LA English

AB Paradoxically, a single injection of recombinant murine interleukin (IL)-12 on the day of bone marrow transplantation (BMT) inhibits graft-vs.-host disease (GVHD) while preserving

graft-vs.-leukemia

(GVL) effects in lethally irradiated mice receiving fully MHC-mismatched bone marrow and spleen cells. These protective effects are mediated by interferon (IFN)-gamma, whose early secretion is induced by IL-12 treatment. We investigated the relationship of IL-12 dose and timing of administration, as well as timing and type of total-body irradiation (TBI), with the ability of IL-12 to inhibit GVHD or mediate toxicity. A relatively low dose of IL-12 (as little as 50 U in a single injection) can mediate significant GVHD protection. The timing of IL-12 administration, however, is a crit. factor. IL-12 administered 1 h before BMT was most protective, but protection was still obsd. when it was administered 1-12 h after BMT. Delaying IL-12 administration to 36 h post-BMT completely obviated its protective effect. Administration of a second IL-12 injection 6 days after BMT negated the protective effect of an initial injection at the time of BMT. While IL-12 protection was evident when TBI was administered by 137Cs-irradiator in one or two fractions on day -1 or day 0, the use of an X-irradiator to deliver TBI on day -1 was assocd. with marked IL-12 toxicity. Whereas the protective effect of IL-12

against GVHD depended on donor-derived IFN- γ , toxicity depended on the ability of host cells to produce IFN- γ . Careful studies are warranted to test the effects of IL-12 in the context of BMT with various conditioning regimens in large animal preclin. models before this novel approach to GVHD protection can be applied clin.

RE.CNT 33

RE

- (1) Allen, R; Eur J Immunol 1993, V23, P333 CAPLUS
- (2) Atkins, M; Clin Cancer Res 1997, V3, P409 CAPLUS
- (3) Berger, M; Transplantation 1994, V57, P1095 CAPLUS
- (4) Blazar, B; J Immunol 1997, V158, P29 CAPLUS
- (5) Blazar, B; Transplantation 1997, V64, P571 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2001 ACS

AN 1998:281943 CAPLUS

DN 128:318898

TI Optimal scheduling of interleukin-12 and fractionated radiation therapy in

the murine Lewis lung carcinoma

AU Teicher, Beverly A.; Ara, Gulshan; Buxton, David; Leonard, John; Schaub, Robert G.

CS Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SO Radiat. Oncol. Invest. (1998), 6(2), 71-80
CODEN: ROINEU; ISSN: 1065-7541

PB Wiley-Liss, Inc.

DT Journal

LA English

AB Interleukin-12 (IL-12), a naturally occurring cytokine, has demonstrated antitumor activity in several murine solid tumors. The Lewis lung carcinoma was used to study the most effective scheduling of recombinant murine interleukin-12 (rmIL-12) administration with fractionated radiation therapy. The effect of the schedule of rmIL-12 administration alone or along with a 1- or 2-wk fractionated radiation therapy regimen was examd. Beginning rmIL-12 prior to or at

the

same time as radiation therapy and extending rmIL-12 through the radiation

regimen and beyond produced the longest tumor growth delays. Those treatment regimens which were most effective against the primary tumor were also most effective in decreasing the no. of lung metastases on day 20. To further assess the immunotherapeutic effects from rmIL-12 administration, the efficacy of rmIL-12 with fractionated radiation therapy delivered to a right hind-limb tumor was measured as tumor growth delay in an unirradiated left hind-limb tumor. There was some difference in the tumor growth delay between the unirradiated tumor in the animals bearing an irradiated tumor in the contralateral leg, and the tumors in animals receiving rmIL-12 only. Recombinant murine

granulocyte-macrophage-

colony stimulating factor (rmGM-CSF) was also an antitumor agent active against the Lewis lung carcinoma and produced an additive effect in combination with fractionated radiation therapy in this tumor. RmIL-12 was a radiation sensitizer in the Lewis lung carcinoma. When rmIL-12 (45-.mu.g/kg) and rmGM-CSF (45 .mu.g/kg) were administered together with fractionated radiation therapy, a marked increase in tumor growth delay resulted. This treatment combination also nearly ablated lung metastases on day 20 in these animals. These results may serve as a useful guide in developing clin. protocols, including rmIL-12 and fractionated radiation therapy.

L6 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS

DUPLICATE 2

AN 1998:80243 BIOSIS

DN PREV199800080243

TI Immunoregulation by interleukin-12 in MB49.1 tumor bearing mice: Cellular

and cytokine-mediated effector mechanisms.

AU Hunter, Sharon E.; Waldburger, Kristine E.; Thibodeaux, Deborah A.; Schaub, Robert G.; **Goldman, Samuel J.; Leonard, John P.**

(1)

CS (1) Genet. Inst., One Burt Rd., Andover, MA 01810 USA

SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3438-3446.
ISSN: 0014-2980.

DT Article

LA English

AB Administration of recombinant murine interleukin (rmIL)-12 to MB49.1 tumor-bearing mice results in dose-dependent regression of the primary tumor and the generation of protective antitumor immunity in the majority of animals. rmIL-12 administration is associated with a marked increase in lymph node cellularity that is predominantly due to the expansion of B220+ B cells as well as CD8+ T cells. Stimulation of lymph node cells from rmIL-12-treated, but not control tumor-bearing mice, with MB49.1 tumor cells in vitro was shown to enhance the secretion of interferon (IFN)-gamma. The magnitude of this in vitro response was dependent on the dose of rmIL-12 administered in vivo and mirrored the change in circulating serum IFN-gamma. Furthermore, at the height of the in vitro response to tumor stimulation, the addition of a neutralizing antibody to murine IL-12 suppressed IFN-gamma production, indicating a role for endogenous IL-12 in this antigen-specific cytokine response. Although studies in SCID mice confirmed that an appropriate T cell response was required for rmIL-12-mediated antitumor activity, in immunocompetent animals early tumor regression was not accompanied by cellular infiltration of the tumor. In contrast, a profound increase in tumor-associated inducible nitric oxide synthase (iNOS) was observed in mice receiving rmIL-12 which preceded T cell infiltration of the tumor which could be detected during the second week of IL-12 treatment. Direct tumor killing through the cytotoxic actions of NO via the iNOS pathway may serve as a way of generating tumor antigen which enables the host to mount a subsequent T cell response against the tumor.

L6 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3

AN 1997:495265 BIOSIS

DN PREV199799794468

TI Effects of single-dose interleukin-12 exposure on interleukin-12-associated toxicity and interferon-gamma production.

AU **Leonard, John P.; Sherman, Matthew L.; Fisher, Gerald L.; Buchanan, Lynn J.; Larsen, Glen; Atkins, Michael B.; Sosman, Jeffrey A.; Dutcher, Janice P.; Vogelzang, Nicholas J.; Ryan, John L.** (1)

CS (1) Genet. Inst., 87 Cambridge Park Dr., Cambridge, MA 02140 USA

SO Blood, (1997) Vol. 90, No. 7, pp. 2541-2548.
ISSN: 0006-4971.

DT Article

LA English

AB Interleukin-12 (IL-12) is a key regulator of cell-mediated immunity that has therapeutic potential in cancer and infectious disease. In a previous Phase 1 dose escalation study of a single test dose of recombinant human IL-12 (rhIL-12) followed 14 days later by cycles of five consecutive daily intravenous injections every 3 weeks, we showed that a dose level up to 500 ng/kg could be administered with acceptable levels of safety. Based on these results, a Phase 2 study was conducted. In the Phase 2 study, however, administration of rhIL-12 at this same dose level resulted in severe toxicities with some patients unable to tolerate more than two successive doses. Of the 17 patients receiving rhIL-12 in the Phase 2 study, 12 patients were hospitalized and two patients died. A thorough scientific investigation to determine the cause of this unexpected toxicity failed to

identify any difference in the drug products used or the patient populations enrolled in the Phase 1 and Phase 2 studies that could have accounted for the profound difference in toxicity. The focus of the investigation therefore shifted to the schedule of rhIL-12

administration.

We determined that a single injection of rhIL-12 2 weeks before consecutive dosing included in the Phase 1 study, but not in the schedule of administration in the Phase 2 study, has a profound abrogating effect on IL-12-induced interferon-gamma (IFN-gamma) production and toxicity. This observation of schedule-dependent toxicity of IL-12 has been verified in mice, as well as nonhuman primates. In this regard, a single injection of IL-12 before consecutive daily dosing protected mice and cynomolgus monkeys from acute toxicity including mortality and was associated with

an

attenuated IFN-gamma response. Because of this unique biologic response, careful attention to the schedule of administration is required to assure safe and effective clinical development of this highly promising

cytokine.

L6 ANSWER 9 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 4

AN 1997:321079 BIOSIS

DN PREV199799611567

TI Interleukin-12 induces relapse in experimental allergic encephalomyelitis in the Lewis rat.

AU Smith, Terence (1); Hewson, Adrian K.; Kingsley, Cherry I.; Leonard, John P.; Cuzner, M. Louise

CS (1) Multiple Sclerosis Lab., Miriam Marks Dep. Neurochem., Inst. Neurol., 1 Wakefield St., London WC1N 1PJ UK

SO American Journal of Pathology, (1997) Vol. 150, No. 6, pp. 1909-1917. ISSN: 0002-9440.

DT Article

LA English

AB Acute, monophasic experimental allergic encephalomyelitis (EAE) in the Lewis rat shows pathological similarities to the human disease multiple sclerosis (MS). Rats that recover from EAE are essentially resistant to disease reinduction, unlike MS in which relapses are frequently associated

with common bacterial and viral infections. As macrophage-derived interleukin (IL)-12 is a critical component of innate resistance to bacterial infection and appears to directly activate encephalitogenic T cells in vivo, the ability of this cytokine to

reinduce

paralysis in EAE was examined. Paralytic disease was exacerbated by intraperitoneal IL-12 administration and could be reinduced up to 1 week after recovery from the primary clinical episode. Concomitant with worsening of initial clinical signs and relapse was an increase in the ratio of macrophages to T cells in brain stem

perivascular

cuffs and the expression of inducible nitric oxide synthase in cells with both macrophage and microglial morphology. These findings suggest that IL-12 may contribute to macrophage-mediated disease exacerbation and relapse in patients with MS.

L6 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2001 ACS

AN 1997:628259 CAPLUS

DN 127:272430

TI Optimal scheduling of interleukin 12 and chemotherapy in the murine MB-49 bladder carcinoma and B16 melanoma

AU Teicher, Beverly A.; Ara, Gulshan; Buxton, David; Leonard, John; Schaub, Robert G.

CS Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA, 02115, USA

SO Clin. Cancer Res. (1997), 3(9), 1661-1667
CODEN: CCREF4; ISSN: 1078-0432

AB The antitumor activity of interleukin (IL)-12, a naturally occurring cytokine, has been demonstrated in several murine solid tumors. Animals bearing established B16 melanoma or MB-49 bladder carcinoma were used to study the most effective scheduling of recombinant murine IL-12 (rmIL-12), along with systemic chemotherapy. RmIL-12 (0.45, 4.5, or 45 .mu.g/kg) was more effective as

a single agent when administered to mice bearing the MB-49 bladder carcinoma

at the highest dose for 11 doses rather than for 5 doses. In combination with chemotherapy (Adriamycin, cyclophosphamide, or 5-fluorouracil), rmIL-12 administration did not increase the toxicity of the chemotherapy, and there was increased antitumor activity with each rmIL-12-drug combination. Administering rmIL-12 (45 .mu.kg) on days 4-14, along with Adriamycin, cyclophosphamide, or 5-fluorouracil on days 7-11, resulted in 2.2-2.7-fold increases in tumor growth delay, compared with the chemotherapy alone against the primary tumor, and a marked decrease in

the no. of lung metastases on day 20. Because the B16 melanoma grows more slowly than the MB-49 bladder carcinoma, allowing multiple courses of chemotherapy, cyclophosphamide could be administered. The rmIL-12 (45 .mu.g/kg)-cyclophosphamide combination regimen that was most effective overlapped 2 days with the terminal portion of the chemotherapy treatment.

There was a parallel increase in the response of the primary tumor and metastatic disease to the lungs. Administration of rmIL-12 to animals bearing the MB-49 bladder carcinoma or the B16 melanoma was compatible with coadministration of chemotherapy at full dose without addnl. toxicity.

L6 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2001 ACS

AN 1998:12658 CAPLUS

DN 128:87479

TI Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12

AU Leonard, John P.; Waldburger, Kristine E.; Schaub, Robert G.; Smith, Terence; Hewson, Adrian K.; Cuzner, M. Louise; Goldman, Samuel J.

CS Genetics Institute, Preclinical Pharmacology, Andover, MA, 01810, USA

SO Crit. Rev. Immunol. (1997), 17(5 & 6), 545-553

CODEN: CCRIDE; ISSN: 1040-8401

PB Begell House, Inc.

DT Journal; General Review

LA English

AB A review with 54 refs. Interleukin 12 (IL-12), a novel heterodimeric protein produced primarily by antigen-presenting cells, serves as a key regulator of innate and adaptive immune responses. In addn. to being a potent inducer of IFN-.gamma., IL-12 is widely considered to be the principal cytokine that regulates the generation of Th1 type effector cells. As the successful induction of exptl. autoimmune encephalomyelitis (EAE) is assocd. with a strong Th1 type cellular response, we have evaluated the role of IL-12 in regulating the pathogenesis of EAE in SJL/J mice and Lewis rats. In both settings, treatment with IL-12 was found to accelerate the onset and increase the severity and duration of clin. disease. More importantly, administration of IL-12 to Lewis rats that had recovered from primary disease was found to trigger clin. relapse. In all instances, IL-12-induced exacerbation was assocd. with a profound increase in iNOS pos. macrophages within the perivascular lesions. Although IL-12-induced IFN-.gamma. does not appear to be required for exacerbation of disease, neutralizing antibodies against murine IL

-12 delay the onset and reduce the severity of adoptively transferred EAE, indicating a role for endogenous IL-12 as regulator of disease. Based on the above findings, effective inhibition of IL-12 in vivo may have great therapeutic value in the treatment of MS and other Th1-assocd. inflammatory disorders.

L6 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 1997:285388 CAPLUS
DN 126:329093
TI Effects of interleukin 12 on hematopoietic stem and progenitor cells
AU Neben, Steven; Leonard, John; Goldman, Samuel;
Ploemacher, Rob E.
CS Department of Immunology and Hematopoiesis, Genetics Institute, Inc.,
Cambridge, MA, USA
SO Bone Marrow Transplant.: Basic Clin. Stud., [Pap. Int. Symp. BMT] (1996),
Meeting Date 1995, 28-35. Editor(s): Ikehara, Susumu; Takaku, Fumimaro;
Good, Robert A. Publisher: Springer, Tokyo, Japan.
CODEN: 64HVAW
DT Conference; General Review
LA English
AB A review with 34 refs. Interleukin-12 (IL-12) has
been shown to possess potent immunomodulatory activity. It has a unique
structure among cytokines, consisting of two covalently linked subunits,
one with homol. to other members of the cytokine superfamily, the other
being highly homologous to gp130, the signaling subunit of a no. of
cytokine receptors. Here we summarize studies showing that IL-
12 is a hematopoietic growth factor with potent activity on
hematopoietic stem and progenitor cells. In clonal and liq. culture
assays, IL-12 synergizes with IL-3 and Steel Factor to
increase the no. of colonies as well as to expand both stem and
progenitor
cell content in the cultures. In stroma-dependent long-term bone marrow
cultures, IL-12 addn. causes a decrease in cell prodn.
in the first week after inoculation of whole bone marrow cells, followed
by an increase in both mature cells and progenitor cells over the next 3
wk. The initial decrease appears to be mediated by IL-
12-induced prodn. of IFN-.gamma., possibly by natural killer cells
and/or T cells which do not persist in these cultures. Studies in naive
mice demonstrate a similar acute decrease in peripheral leukocyte count,
mediated by IFN-.gamma., upon administration of IL-12.
In contrast, despite a significant decrease in peripheral platelet count,
reticulated platelets become elevated and mean megakaryocyte ploidy in
the
bone marrow shifts from 16N to 32N during IL-12
treatment. These IL-12-mediated effects on
megakaryopoiesis are abrogated by simultaneous treatment of mice with
antibodies against IFN-.gamma.. These studies provide further
information
on the potential physiol. role and applications of IL-12
outside the immune system.

L6 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 1995:934127 CAPLUS
DN 123:337469
TI Use of IL-12 and IL-12 antagonists
in treatment of autoimmune diseases
IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard,
Jr.
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		
AB	Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering IL-12 or an IL-12 antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice.				
The	injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12.				
L6	ANSWER 14 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5				
AN	1996:74926 BIOSIS				
DN	PREV199698647061				
TI	Structural characterization of the recombinant P40 heavy chain subunit monomer and homodimer of murine IL-12.				
AU	Nickbarg, Elliott B. (1); Vath, James E.; Pittman, Debra D.; Leonard, John E.; Waldburger, Kristine E.; Bond, Michael D.				
CS	(1) Genetics Inst. Inc., 87 Cambridgepark Drive, Cambridge, MA 02140 USA				
SO	Bioorganic Chemistry, (1995) Vol. 23, No. 4, pp. 380-396.				
	ISSN: 0045-2068.				
DT	Article				
LA	English				
AB	Interleukin-12 (IL-12) is a heterodimeric cytokine that consists of two structurally unrelated subunits, P35 and P40. However, when expressed alone in Chinese hamster ovary (CHO) cells, murine P40 showed two species of different molecular weights under nonreducing conditions, a monomeric form of 45 kDa and a homodimer of gt 97 kDa.				
Under	reducing conditions the two forms migrated as an identical array of species of 40-45 kDa. The monomer was separated from the homodimer under nonreducing conditions by heparin affinity chromatography and the disulfide bond structures of both species were determined by peptide mapping. Edman sequencing, and mass spectrometry. The peptide maps of the two species were identical except for a single peak that changed retention time. Sequencing showed that this peak contained two peptides of identical sequences in both maps. Mass spectrometric analysis of the peak from the gt 97-kDa species revealed an ion of double the expected mass, thus indicating that the peptide pair had dimerized. Mass analysis of the peak from the 40- to 45-kDa species showed that the peptide pair contained a mass difference that corresponded to that of an extra cysteine and which				

disappeared upon reduction. Amino acid analysis confirmed that the monomeric form of rmp40 is modified by a reducible cysteine. Structural analysis of the remainder of the cysteine-containing peaks showed that both species of rmp40 contained the same set of intramolecular disulfide bonds. The murine P40 homodimer arises from formation of a single intermolecular disulfide bond at Cys-175. In the monomeric P40, however, this cysteine is capped by an additional cysteine. Purified rmp40 monomer and homodimer inhibited the IL-12-dependent induction of interferon-gamma, but neither appeared capable of inducing IL-12-like biological activity.

L6 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6

AN 1993:343704 BIOSIS

DN PREV199396040704

TI Resolution of cutaneous leishmaniasis: Interleukin 12 initiates a protective T helper type 1 immune response.

AU Sypek, Joseph P. (1); Chung, Charles L.; Mayor, Sharon E. H.; Subramanyam,

Janaki M.; Goldman, Samuel L.; Sieburth, Derek S.; Wolf, Stanley F.; Schaub, Robert G.

CS (1) Dep. Preclin. Biol., Genetics Inst. Inc., 87 Cambridge Park Dr., Cambridge, MA 02140 USA

SO Journal of Experimental Medicine, (1993) Vol. 177, No. 6, pp. 1797-1802. ISSN: 0022-1007.

DT Article

LA English

AB Resistance to *Leishmania major* in mice is associated with the appearance of distinct T helper type 1 (Th1) and Th2 subsets. T cells from lymph nodes draining cutaneous lesions of resistant mice are primarily interferon γ (IFN- γ)-producing Th1 cells. In contrast, T cells from susceptible mice are principally Th2 cells that generate interleukin 4 (IL-4). Although existing evidence is supportive of a role for IFN- γ in the generation of Th1 cells, additional factors may be required for a protective response to be maintained. A potential candidate is IL-12, a heterodimeric cytokine produced by monocytes and B cells that has multiple effects on T and natural killer cell function,

including

inducing IFN- γ production. Using an experimental leishmanial model we have observed that daily intraperitoneal administration at the time of parasite challenge of either 0.33 μ -g IL-12 (a consecutive 5 d/wk for 5 wk) or 1.0 μ -g IL-12 per mouse (only a consecutive 5 d) caused a \geq 75% reduction in parasite burden at the site of infection, in highly susceptible BALB/c mice. Delay of treatment by 1 wk had less of a protective effect. Concomitant with these protective effects was an increase in IFN- γ and a decrease in IL-4 production, as measured by enzyme-linked immunosorbent assay of supernatants generated from popliteal lymph node cells stimulated with leishmanial antigen in vitro. The reduction in parasite numbers induced

by

IL-12 therapy was still apparent at 10 wk postinfection. In addition, we observed that the administration of a rabbit anti-recombinant murine IL-12 polyclonal antibody (200 μ -g i.p. every other day for 25 d) at the time of infection to resistant C57Bl/6 mice exacerbated disease. These effects were accompanied by a shift in IFN- γ production in vitro by antigen-stimulated lymph node cells indicative of a Th2-like response. These findings suggest that IL-12 has an important role in initiating a Th1 response and protective immunity.

=> s 14 and multiple sclerosis

L7 8 L4 AND MULTIPLE SCLEROSIS

=> dup rem 17

=> d bib ab 1-6

L8 ANSWER 1 OF 6 USPATFULL
AN 2000:74115 USPATFULL
TI Polynucleotides encoding human CTLA-8 related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States
Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S.
corporation)
PI US 6074849 20000613
AI US 1996-685239 19960718 (8)
RLI Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
DT Utility
EXNAM Primary Examiner: Draper, Garnette D.
LREP Brown, Scott A.; Sprunger, Suzanne A.; DesRosier, Thomas J.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1658
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polynucleotides encoding human CTLA-8 related proteins are disclosed.
Human CTLA-8 proteins and methods for their production are also
disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8
proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L8 ANSWER 2 OF 6 USPATFULL
AN 2000:37900 USPATFULL
TI Human CTLA-8 and uses of CTLA-8-related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States
Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S.
corporation)
PI US 6043344 20000328
AI US 1998-34810 19980304 (9)
RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now
abandoned
which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19
Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014,
filed on 11 Aug 1995, now patented, Pat. No. US 5707829
PRAI US 1995-35347 19950719 (60)
DT Utility
EXNAM Primary Examiner: Draper, Garnette D.
LREP Lahive & Cockfield, LLP; Mandragouras, Esq., Amy E.; Lauro, Esq., Peter
C.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Polynucleotides encoding human CTLA-8 and related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L8 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2001 ACS

AN 2000:573837 CAPLUS

DN 133:191991

TI Humanized immunoglobulin reactive with B7 molecules and methods of treatment therewith

IN Co, Man Sung; Vasquez, Maximiliano; Carreno, Beatriz; Celniker, Abbie Cheryl; Collins, Mary; **Goldman, Samuel**; Gray, Gary S.; Knight, Andrea; O'Hara, Denise; Rup, Bonita; Veldman, Geertruida M.

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 162 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000047625	A2	20000817	WO 2000-US3303	20000209
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRAI US 1999-249011 19990212

US 1999-339596 19990624

AB The invention relates to humanized anti-B7-2 and anti-B7-1 antibodies, wherein each comprise a variable region of non-human origin and at least

a

portion of an Ig of human origin. The invention also pertains to methods of treatment for various autoimmune diseases, transplant rejection, inflammatory disorders and infectious diseases by administering humanized anti-B7-2 and/or anti-B7-1 antibodies.

L8 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1

AN 1997:321079 BIOSIS

DN PREV199799611567

TI Interleukin-12 induces relapse in experimental allergic encephalomyelitis in the Lewis rat.

AU Smith, Terence (1); Hewson, Adrian K.; Kingsley, Cherry I.; **Leonard, John P.**; Cuzner, M. Louise

CS (1) Multiple Sclerosis Lab., Miriam Marks Dep. Neurochem., Inst. Neurol., 1 Wakefield St., London WC1N 1PJ UK

SO American Journal of Pathology, (1997) Vol. 150, No. 6, pp. 1909-1917. ISSN: 0002-9440.

DT Article

LA English

AB Acute, monophasic experimental allergic encephalomyelitis (EAE) in the Lewis rat shows pathological similarities to the human disease **multiple sclerosis** (MS). Rats that recover from EAE are essentially resistant to disease reinduction, unlike MS in which relapses are frequently associated with common bacterial and viral infections. As macrophage-derived interleukin (IL)-12 is a critical component of innate resistance to bacterial infection and appears to directly activate

encephalitogenic T cells in vivo, the ability of this cytokine to reinduce paralysis in EAE was examined. Paralytic disease was exacerbated by intraperitoneal IL-12 administration and could be reinduced up to 1 week after recovery from the primary clinical episode. Concomitant with worsening of initial clinical signs and relapse was an increase in the ratio of macrophages to T cells in brain stem perivascular cuffs and the expression of inducible nitric oxide synthase in cells with both macrophage and microglial morphology. These findings suggest that IL-12 may contribute to macrophage-mediated disease exacerbation and relapse in patients with MS.

L8 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
 AN 1998:55862 BIOSIS
 DN PREV199800055862
 TI Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12.
 AU Leonard, John P. (1); Waldburger, Kristine E. (1); Schaub, Robert G. (1); Smith, Terence; Hewson, Adrian K.; Cuzner, M. Louis; Goldman, Samuel J. (1)
 CS (1) Genetics Inst. Preclinical Pharmacology, Andover, MA 01810 USA
 SO Critical Reviews in Immunology, (1997) Vol. 17, No. 5-6, pp. 545-553. ISSN: 1040-8401.
 DT General Review
 LA English

L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
 AN 1995:934127 CAPLUS
 DN 123:337469
 TI Use of IL-12 and IL-12 antagonists in treatment of autoimmune diseases
 IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.
 PA Genetics Institute, Inc., USA
 SO PCT Int. Appl., 37 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		
AB	Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering IL-12 or an IL-12 antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of				

these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12.

=> s 14 and antagonist?

L9 5 L4 AND ANTAGONIST?

=> dup rem 19

PROCESSING COMPLETED FOR L9

L10 4 DUP REM L9 (1 DUPLICATE REMOVED)

=> d bib ab 1-4

L10 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS

AN 2000:573837 CAPLUS

DN 133:191991

TI Humanized immunoglobulin reactive with B7 molecules and methods of treatment therewith

IN Co, Man Sung; Vasquez, Maximiliano; Carreno, Beatriz; Celniker, Abbie Cheryl; Collins, Mary; **Goldman, Samuel**; Gray, Gary S.; Knight, Andrea; O'Hara, Denise; Rup, Bonita; Veldman, Geertruida M.

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 162 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000047625	A2	20000817	WO 2000-US3303	20000209
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRAI US 1999-249011 19990212

US 1999-339596 19990624

AB The invention relates to humanized anti-B7-2 and anti-B7-1 antibodies, wherein each comprise a variable region of non-human origin and at least

a portion of an Ig of human origin. The invention also pertains to methods of treatment for various autoimmune diseases; transplant rejection, inflammatory disorders and infectious diseases by administering humanized anti-B7-2 and/or anti-B7-1 antibodies.

L10 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS

AN 1995:934127 CAPLUS

DN 123:337469

TI Use of IL-12 and IL-12 antagonists in treatment of autoimmune diseases

IN **Leonard, John P.**; **Goldman, Samuel**; O'Hara, Richard, Jr.

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		
AB	Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN- γ or TNF- α , are treated in mammals by administering IL-12 or an IL-12 antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12.				
L10	ANSWER 3 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1				
AN	1994:181703 BIOSIS				
DN	PREV199497194703				
TI	Effects of nitroprusside and redox reagents on NMDA receptors expressed in				
	Xenopus oocytes.				
AU	Omerovic, Azra; Leonard, John P.; Kelso, Stephen R. (1)				
CS	(1) Dep. Biol. Sci., Univ. Ill. at Chicago, Chicago, IL 60680 USA				
SO	Molecular Brain Research, (1994) Vol. 22, No. 1-4, pp. 89-96. ISSN: 0169-328X.				
DT	Article				
LA	English				
AB	We have examined the effects of oxidizing and reducing agents and sodium nitroprusside (SNP) on currents evoked by NMDA (N-methyl-Daspartate) using				
	the Xenopus oocyte expression system. Oocytes were injected with RNA prepared from either whole rat brain or from the NMDAR1 clone recently isolated from rat brain. Bath application of 1-1000 μ M SNP, which releases nitric oxide and ferrocyanide, caused a rapid inhibition of NMDA-evoked current in both preparations. The inhibitory effect reversed spontaneously within 15 min. Kainate responses were not affected by SNP. Exposure to the reducing agent, dithiothreitol (DTT), enhanced NMDA currents; the oxidant, 5,5-dithio-bis-2-nitrobenzoic acid (DTNB), inhibited NMDA responses, as has been observed in other preparations. The site of action of SNP appeared to be different than the DTT/DTNB redox site for several reasons: SNP and DTNB inhibitions were additive at high doses, DTT did not rapidly reverse SNP effects, and SNP and DTT treatments				
	did not show the same susceptibility to block by the NMDA antagonist, aminophosphonovaleric acid (APV). The results demonstrate that modulation of NDMA receptors by SNP is a property of homomeric channels and is retained when the NMDAR1 subunit is expressed in				
	oocytes.				
L10	ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS				

AN 1987:193524 CAPLOS
 DN 106:193524
 TI Calcium channels induced in Xenopus oocytes by rat brain mRNA
 AU Leonard, John P.; Nargeot, Joel; Snutch, Terry P.; Davidson, Norman; Lester, Henry A.
 CS Div. Biol., California Inst. Technol., Pasadena, CA, 91125, USA
 SO J. Neurosci. (1987), 7(3), 875-81
 CODEN: JNRSDS; ISSN: 0270-6474
 DT Journal
 LA English
 AB RNA was isolated from brains of 16-day-old rats and poly(A) samples were injected into stage V and VI oocytes. After allowing 2-5 days for expression, most oocytes were exposed to medium in which the K⁺ had been replaced by Cs⁺ for 24 h prior to recording. Ba²⁺ currents (IBas) were usually measured in Cl⁻-free Ba²⁺ methanesulfonate saline. The IBa in noninjected oocytes was often undetectable, but ranged 0-50 nA (mean 22 nA). In contrast, injected oocytes showed a peak IBa of 339 nA. The threshold for activation of IBa was -40 mV, with peak currents at +10 to +20 mV. After a peak, currents decayed to a nearly steady level along a single-exponential time course (time const. = 650 ms at +20 mV). The maintained current was 67% of the early peak amplitude. A prepulse duration of 5 s was needed to examine the inactivation of IBas in injected oocytes. The inward IBa could be obsd. in BaCl₂ solns. at potentials pos. to the Cl⁻ potential and also in Na⁺-free salines, indicating that neither Cl⁻ nor Na⁺ was carrying the inward current. Although IBa displayed voltage-independent blockade by Cd²⁺ (50% inhibition at 6 .mu.m), the peptide Ca²⁺-channel antagonist Conus geographus .omega.-toxin (1 .mu.M) and the org. Ca²⁺ channel-blocking agents (verapamil, W-7, and nifedipine) were uniformly ineffective. No effects were obsd. with the dihydropyridine antagonist nifedipine (even at 10 .mu.M, or when cells were held at -40 mV) or agonist Bay K-8644. However, IBa was enhanced via activation of protein kinase C with 4-.beta.-phorbol dibutyrate. In contrast, the use of forskolin to activate protein kinase A did not alter IBa. However, expts. in the presence of Cd²⁺ revealed that forskolin decreased IK. Ca²⁺ channels produced by rat brain mRNA were thus in contrast to the nifedipine-sensitive, Bay K-8644- and forskolin-enhanced Ca²⁺ channels obsd. after injection of rat heart mRNA.

=> s l4 and rheumatoid arthritis

L11 3 L4 AND RHEUMATOID ARTHRITIS

=> dup rem l11

PROCESSING COMPLETED FOR L11

L12 3 DUP REM L11 (0 DUPLICATES REMOVED)

=> d bib ab 1-3

L12 ANSWER 1 OF 3 USPATFULL

AN 2000:74115 USPATFULL

TI Polynucleotides encoding human CTLA-8 related proteins

IN Jacobs, Kenneth, Newton, MA, United States

Kelleher, Kerry, Marlborough, MA, United States

Carlin, McKeough, Cambridge, MA, United States

Goldman, Samuel, Acton, MA, United States

Pittman, Debra, Windham, NH, United States

Mi, Sha, Belmont, MA, United States

Neben, Steven, Acton, MA, United States

Giannotti, Joanne, Acton, MA, United States

PA Golden-Fleet, Margaret M., Medford, MA, United States (U.S. Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation))
 PI US 6074849 20000613
 AI US 1996-685239 19960718 (8)
 RLI Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Brown, Scott A.; Sprunger, Suzanne A.; DesRosier, Thomas J.
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
 LN.CNT 1658
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Polynucleotides encoding human CTLA-8 related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L12 ANSWER 2 OF 3 USPATFULL
 AN 2000:37900 USPATFULL
 TI Human CTLA-8 and uses of CTLA-8-related proteins
 IN Jacobs, Kenneth, Newton, MA, United States
 Kelleher, Kerry, Marlborough, MA, United States
 Carlin, McKeough, Cambridge, MA, United States
 Goldman, Samuel, Acton, MA, United States
 Pittman, Debra, Windham, NH, United States
 Mi, Sha, Belmont, MA, United States
 Neben, Steven, Acton, MA, United States
 Giannotti, Joanne, Acton, MA, United States
 Golden-Fleet, Margaret M., Medford, MA, United States
 PA Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)
 PI US 6043344 20000328
 AI US 1998-34810 19980304 (9)
 RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now abandoned
 which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19 Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995, now patented, Pat. No. US 5707829
 PRAI US 1995-35347 19950719 (60)
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Lahive & Cockfield, LLP; Mandragouras, Esq., Amy E.; Lauro, Esq., Peter C.
 CLMN Number of Claims: 13
 ECL Exemplary Claim: 1
 DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
 LN.CNT 1761
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Polynucleotides encoding human CTLA-8 and related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L12 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
 AN 1995:934127 CAPLUS
 DN 123:337469
 TI Use of IL-12 and IL-12 antagonists in treatment of autoimmune diseases
 IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.
 PA Genetics Institute, Inc., USA
 SO PCT Int. Appl., 37 pp.
 CODEN: PIXXD2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		
AB	Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis , autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering IL-12 or an IL-12 antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12.				

=> d clm 1

L12 ANSWER 1 OF 3 USPATFULL

CLM What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (a) the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544; and (b) a nucleotide sequence varying from the sequence of the nucleotide sequence specified in (a) as a result of degeneracy of the genetic code.
2. The polynucleotide of claim 1 wherein said nucleotide sequence is operably linked to an expression control sequence.
3. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 55 to nucleotide 544.
4. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 86 to nucleotide 544.
5. The polynucleotide of claim 2 wherein said polynucleotide is contained in a vector suitable for in vivo expression in a mammalian subject.
6. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 139 to nucleotide 544.
7. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544.

8. A host cell transformed with the polynucleotide of claim 2.

9. The host cell of claim 8, wherein said cell is a mammalian cell.

10. A process for producing a human CTLA-8 protein, said process comprising: (a) growing a culture of the host cell of claim 8 in a suitable culture medium; and (b) purifying the human CTLA-8 protein from the culture.

=> d clm 3

'CLM' IS NOT A VALID FORMAT

In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):.

L12 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS

AN 1995:934127 CAPLUS

DN 123:337469

TI Use of IL-12 and IL-12 antagonists in treatment of autoimmune diseases

IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		

=> s 14 and interferon

L13 24 L4 AND INTERFERON

=> dup rem 113

PROCESSING COMPLETED FOR L13

L14 17 DUP REM L13 (7 DUPLICATES REMOVED)

=> d bib ab 1-18

L14 ANSWER 1 OF 17 USPATFULL
 AN 2000:74115 USPATFULL
 TI Polynucleotides encoding human CTLA-8 related proteins
 IN Jacobs, Kenneth, Newton, MA, United States
 Kelleher, Kerry, Marlborough, MA, United States
 Carlin, McKeough, Cambridge, MA, United States
 Goldman, Samuel, Acton, MA, United States
 Pittman, Debra, Windham, NH, United States
 Mi, Sha, Belmont, MA, United States
 Neben, Steven, Acton, MA, United States
 Giannotti, Joanne, Acton, MA, United States
 Golden-Fleet, Margaret M., Medford, MA, United States
 PA Genetics Institute, Inc., Cambridge, MA, United States (U.S.
 corporation)
 PI US 6074849 20000613
 AI US 1996-685239 19960718 (8)
 RLI Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Brown, Scott A.; Sprunger, Suzanne A.; DesRosier, Thomas J.
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
 LN.CNT 1658
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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 Human CTLA-8 proteins and methods for their production are also
 disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8
 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L14 ANSWER 2 OF 17 USPATFULL
 AN 2000:37900 USPATFULL
 TI Human CTLA-8 and uses of CTLA-8-related proteins
 IN Jacobs, Kenneth, Newton, MA, United States
 Kelleher, Kerry, Marlborough, MA, United States
 Carlin, McKeough, Cambridge, MA, United States
 Goldman, Samuel, Acton, MA, United States
 Pittman, Debra, Windham, NH, United States
 Mi, Sha, Belmont, MA, United States
 Neben, Steven, Acton, MA, United States
 Giannotti, Joanne, Acton, MA, United States
 Golden-Fleet, Margaret M., Medford, MA, United States
 PA Genetics Institute, Inc., Cambridge, MA, United States (U.S.
 corporation)
 PI US 6043344 20000328
 AI US 1998-34810 19980304 (9)
 RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now
 abandoned
 which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19
 Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014,
 filed on 11 Aug 1995, now patented, Pat. No. US 5707829
 PRAI US 1995-35347 19950719 (60)
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Lahive & Cockfield, LLP; Mandragouras, Esq., Amy E.; Lauro, Esq., Peter
 C.
 CLMN Number of Claims: 13
 ECL Exemplary Claim: 1
 DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
 LN.CNT 1761
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Polynucleotides encoding human CTLA-8 and related proteins are
 disclosed. Human CTLA-8 proteins and methods for their production are
 also disclosed. Methods of treatment using human CTLA-8 proteins, rat
 CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also

L14 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2001 ACS

AN 1999:736789 CAPLUS

DN 132:48827

TI Autocrine regulation of IL-12 receptor expression is independent of secondary IFN-.gamma. secretion and not restricted to T and NK cells

AU Thibodeaux, Deborah K.; Hunter, Sharon E.; Waldburger, Kristine E.;

Bliss,

Judy L.; Trepicchio, William L.; Sypek, Joseph P.; Dunussi-Joannopoulos, Kyriaki; Goldman, Samuel J.; Leonard, John P.

CS Preclinical Research and Development, Genetics Institute, Andover, MA, 01810, USA

SO J. Immunol. (1999), 163(10), 5257-5264

CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists

DT Journal

LA English

AB The biol. response to IL-12 is mediated through specific binding to a high

affinity receptor complex composed of at least two subunits (designated IL-12R.beta.1 and IL-12R.beta.2) that are expressed on NK cells and activated T cells. The selective loss of IL-12R.beta.2 expression during Th2 T cell differentiation suggests that regulation of this receptor component may govern IL-12 responsiveness. In murine assays, down-regulation of IL-12R.beta.2 expression can be prevented by treatment with IFN-.gamma., indicating that receptor expression and hence IL-12 responsiveness may be regulated, at least in part, by the local cytokine milieu. In this study, the authors report that cellular expression of both IL-12R.beta.1 and .beta.2 mRNA is increased in the lymph nodes of naive mice following systemic administration of murine rIL-12 (rmIL-12). Changes in IL-12R mRNA were assocd. with increased IFN-.gamma. secretion following ex vivo activation of lymph node cells with rmIL-12, indicating the presence of a functional receptor complex. Expression of IL-12R mRNA was not restricted to lymph node T cells, and its autocrine regulation

was

independent of secondary IFN-.gamma. secretion. Data from fractionated lymph node cells as well as rmIL-12-treated B cell-deficient mice suggest that IL-12-responsive B cells may represent an alternative cellular

source

for IFN-.gamma. prodn. However, the strength of the biol. response to rmIL-12 is not governed solely by receptor expression, as rmIL-12-induced IFN-.gamma. secretion from cultured lymph node cells is accessory cell dependent and can be partially blocked by inhibition of B7 costimulation.

RE.CNT 40

RE

(1) Cella, M; J Exp Med 1996, V184, P747 CAPLUS

(2) Chan, S; J Exp Med 1991, V173, P869 CAPLUS

(3) Chizzonite, R; J Immunol 1992, V148, P3117 CAPLUS

(4) de Kruffy, R; J Immunol 1997, V158, P359 CAPLUS

(5) Desai, B; J Immunol 1992, V148, P3125 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS

DUPLICATE 1

AN 2000:59937 BIOSIS

DN PREV200000059937

TI Vaccines with interleukin-12-transduced acute myeloid leukemia cells elicit very potent therapeutic and long-lasting protective immunity.

AU Dunussi-Joannopoulos, Kyriaki (1); Runyon, Kathlene; Erickson, Jamie; Schaub, Robert G.; Hawley, Robert G.; Leonard, John P.

CS (1) Genetics Institute, 1 Burt Rd, Andover, MA USA

SO Blood, (Dec. 15, 1999) Vol. 94, No. 12, pp. 4263-4273.

ISSN: 0006-4971.

DT Article

LA English

SI English
 AB Interleukin-12 (IL-12) is a heterodimeric cytokine mediating a dynamic
 interplay between T cells and antigen-presenting cells (APCs).
 Preclinical
 studies have demonstrated that recombinant murine IL-12 (rmIL-12)
 promotes
 specific antitumor immunity mediated by T cells in several types of
 tumors. However, the in vivo antitumor properties of IL-12 in acute
 myeloid leukemia (AML) have not been previously reported. We show here in
 a murine AML model that systemic administration of rmIL-12 significantly
 delays tumor growth but is incapable of rescuing mice from lethal
 leukemia. In contrast, AML cells genetically modified to express IL-12
 (IL12-AML) using murine stem cell virus (MSCV) p40 + p35 elicit very
 potent antileukemic activity. Vaccines with lethally irradiated IL12-AML
 cells protect naive mice against challenge with wild-type AML cells and,
 more importantly, can cure mice bearing a considerable leukemic burden.
 Immunized mice show no signs of systemic IL-12 toxicity and their spleen
 histology is comparable with naive mice spleen. In vivo depletion of
 IL-12, **interferon-gamma** (IFN-gamma), or CD8+ T cells after
 injections with live IL12-AML cells abrogates completely the antileukemia
 immune responses. Studies on the in vitro effects of IFN-gamma on AML
 cells demonstrate enhanced expression of major histocompatibility complex
 (MHC) and accessory molecules and induction of the costimulatory
 molecules
 B7.1 and B7.2, but no significant direct antiproliferative effect. 51Cr
 release assays show that rejection of live IL12-AML cells supports the
 development of long-lasting leukemia-specific cytotoxic T lymphocyte
 (CTL)
 activity. In conclusion, our results demonstrate that IL12-AML
 vaccination
 is a safe and potent immunotherapeutic approach that has a great
 potential
 to eliminate minimal residual disease in patients with AML.

L14 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2001 ACS

AN 2000:177320 CAPLUS

DN 133:191823

TI Dose and timing of interleukin (IL)-12 and timing and type of total-body
 irradiation: effects on graft-vs.-host disease inhibition and toxicity of
 exogenous IL-12 in murine bone marrow transplant recipients

AU Sykes, Megan; Pearson, Denise A.; Taylor, Patricia A.; Szot, Gregory L.;
Goldman, Samuel J.; Blazar, Bruce R.

CS BMT Section, Transplantation Biology Research Center, Surgical Service,
 Massachusetts General Hospital/Harvard Medical School, Boston, MA, 02129,
 USA

SO Biol. Blood Marrow Transplant. (1999), 5(5), 277-284
 CODEN: BBMTF6; ISSN: 1083-8791

PB Carden Jennings Publishing

DT Journal

LA English

AB Paradoxically, a single injection of recombinant murine interleukin
 (IL)-12 on the day of bone marrow transplantation (BMT) inhibits
 graft-vs.-host disease (GVHD) while preserving graft-vs.-leukemia (GVL)
 effects in lethally irradiated mice receiving fully MHC-mismatched bone
 marrow and spleen cells. These protective effects are mediated by
interferon (IFN)-gamma, whose early secretion is induced by
 IL-12 treatment. We investigated the relationship of IL-12 dose and
 timing of administration, as well as timing and type of total-body

irradn.
 (TBI), with the ability of IL-12 to inhibit GVHD or mediate toxicity. A
 relatively low dose of IL-12 (as little as 50 U in a single injection)

can
 mediate significant GVHD protection. The timing of IL-12 administration,
 however, is a crit. factor. IL-12 administered 1 h before BMT was most
 protective, but protection was still obsd. when it was administered 1-12

h

after BMT. Delaying IL-12 administration to 36 h post-BMT completely obviated its protective effect. Administration of a second IL-12 injection 6 days after BMT negated the protective effect of an initial injection at the time of BMT. While IL-12 protection was evident when

TBI

was administered by 137Cs-irradiator in one or two fractions on day -1 or day 0, the use of an X-irradiator to deliver TBI on day -1 was assocd. with marked IL-12 toxicity. Whereas the protective effect of IL-12 against GVHD depended on donor-derived IFN- γ , toxicity depended on the ability of host cells to produce IFN- γ . Careful studies are warranted to test the effects of IL-12 in the context of BMT with various conditioning regimens in large animal preclin. models before this novel approach to GVHD protection can be applied clin.

RE.CNT 33

RE

- (1) Allen, R; Eur J Immunol 1993, V23, P333 CAPLUS
- (2) Atkins, M; Clin Cancer Res 1997, V3, P409 CAPLUS
- (3) Berger, M; Transplantation 1994, V57, P1095 CAPLUS
- (4) Blazar, B; J Immunol 1997, V158, P29 CAPLUS
- (5) Blazar, B; Transplantation 1997, V64, P571 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:46829 BIOSIS

DN PREV200000046829

TI Oligonucleotide microarray analysis of murine acute myeloid leukemia (AML)

cells after in vitro exposure to IFN- γ : Gene expression profiling in activation-induced cell death (AICD).

AU Johnson, Joyce (1); Leppanen, Scott (1); Clancy, Brian (1); Leonard, John (1); Dunussi-Joannopoulos, Kyriaki (1)

CS (1) Tumor Immunology, Genetics Institute, Inc., Andover, MA USA

SO Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 79a.
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.

DT Conference

LA English

L14 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2001 ACS

AN 1997:211225 CAPLUS

DN 126:198563

TI Human cytotoxic T-lymphocyte-activating antigen 8 and a cDNA encoding it
IN Jacobs, Kenneth; Kelleher, Kerry; Carlin, McKeough; Goldman, Samuel; Pittman, Debra; Mi, Sha; Neben, Steven; Giannotti, Joann; Golden-Fleet, Margaret

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9704097	A2	19970206	WO 1996-US11889	19960718
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,				
SE	US 5707829	A	19980113	US 1995-514014	19950811
	AU 9667123	A1	19970218	AU 1996-67123	19960218
	AU 727480	B2	20001214		
	CA 2227220	AA	19970206	CA 1996-2227220	19960718
	EP 839196	A2	19980506	EP 1996-927237	19960718
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

JP 11510045 T2 19990907 JP 1996-506846 19960718

PRAI US 1995-504032 19950719
 US 1995-514014 19950811
 WO 1996-US11889 19960718

AB A cDNA encoding human CTLA-8 (cytotoxic T-lymphocyte-activating antigen 8)
 is cloned and the cDNA and the gene product are characterized. The cDNA can be used in the manuf. of the antigen. Methods of treatment of diseases using human CTLA-8 proteins are described. Rat and herpesvirus CTLA-8 proteins are also described. Cloning and expression of a human cDNA using COS cells as expression host is demonstrated. Human CTLA-8 was shown to inhibit angiogenesis and to stimulate hematopoiesis. Mice infected with an adenovirus expressing the human CTLA-8 cDNA showed increased levels of hematopoietic precursor cells.

L14 ANSWER 8 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
 AN 1998:80243 BIOSIS
 DN PREV199800080243
 TI Immunoregulation by interleukin-12 in MB49.1 tumor bearing mice: Cellular and cytokine-mediated effector mechanisms.
 AU Hunter, Sharon E.; Waldburger, Kristine E.; Thibodeaux, Deborah K.; Schaub, Robert G.; Goldman, Samuel J.; Leonard, John P.
 (1)
 CS (1) Genet. Inst., One Burtt Rd., Andover, MA 01810 USA
 SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3438-3446.
 ISSN: 0014-2980.
 DT Article
 LA English
 AB Administration of recombinant murine interleukin (rmIL)-12 to MB49.1 tumor-bearing mice results in dose-dependent regression of the primary tumor and the generation of protective antitumor immunity in the majority of animals. rmIL-12 administration is associated with a marked increase in lymph node cellularity that is predominantly due to the expansion of B220+ B cells as well as CD8+ T cells. Stimulation of lymph node cells from rmIL-12-treated, but not control tumor-bearing mice, with MB49.1 tumor cells in vitro was shown to enhance the secretion of interferon (IFN)-gamma. The magnitude of this in vitro response was dependent on the dose of rmIL-12 administered in vivo and mirrored the change in circulating serum IFN-gamma. Furthermore, at the height of the in vitro response to tumor stimulation, the addition of a neutralizing antibody to murine IL-12 suppressed IFN-gamma production, indicating a role for endogenous IL-12 in this antigen-specific cytokine response. Although studies in SCID mice confirmed that an appropriate T cell response was required for rmIL-12-mediated antitumor activity, in immunocompetent animals early tumor regression was not accompanied by cellular infiltration of the tumor. In contrast, a profound increase in tumor-associated inducible nitric oxide synthase (iNOS) was observed in mice receiving rmIL-12 which preceded T cell infiltration of the tumor which could be detected during the second week of IL-12 treatment. Direct tumor killing through the cytotoxic actions of NO via the iNOS pathway may serve as a way of generating tumor antigen which enables the host to mount a subsequent T cell response against the tumor.

L14 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
 AN 1997:495265 BIOSIS
 DN PREV199799794468
 TI Effects of single-dose interleukin-12 exposure on interleukin-12-associated toxicity and interferon-gamma production.

AU **Leonard, John P.**; Okumura, Matthew I.; Fisher, Gerald L.; Buchanan, Lynn J.; Larsen, Glen; Atkins, Michael B.; Sosman, Jeffrey A.; Dutcher, Janice P.; Vogelzang, Nicholas J.; Ryan, John L. (1)
 CS (1) Genet. Inst., 87 Cambridge Park Dr., Cambridge, MA 02140 USA
 SO Blood, (1997) Vol. 90, No. 7, pp. 2541-2548.
 ISSN: 0006-4971.
 DT Article
 LA English
 AB Interleukin-12 (IL-12) is a key regulator of cell-mediated immunity that has therapeutic potential in cancer and infectious disease. In a previous Phase 1 dose escalation study of a single test dose of recombinant human IL-12 (rhIL-12) followed 14 days later by cycles of five consecutive daily intravenous injections every 3 weeks, we showed that a dose level up to 500 ng/kg could be administered with acceptable levels of safety. Based on these results, a Phase 2 study was conducted. In the Phase 2 study, however, administration of rhIL-12 at this same dose level resulted in severe toxicities with some patients unable to tolerate more than two successive doses. Of the 17 patients receiving rhIL-12 in the Phase 2 study, 12 patients were hospitalized and two patients died. A thorough scientific investigation to determine the cause of this unexpected toxicity failed to identify any difference in the drug products used or the patient populations enrolled in the Phase 1 and Phase 2 studies that could have accounted for the profound difference in toxicity. The focus of the investigation therefore shifted to the schedule of rhIL-12 administration. We determined that a single injection of rhIL-12 2 weeks before consecutive dosing included in the Phase 1 study, but not in the schedule of administration in the Phase 2 study, has a profound abrogating effect on IL-12-induced **interferon-gamma** (IFN-gamma) production and toxicity. This observation of schedule-dependent toxicity of IL-12 has been verified in mice, as well as nonhuman primates. In this regard, a single injection of IL-12 before consecutive daily dosing protected mice and cynomolgus monkeys from acute toxicity including mortality and was associated with an attenuated IFN-gamma response. Because of this unique biologic response, careful attention to the schedule of administration is required to assure safe and effective clinical development of this highly promising cytokine.

L14 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1998:55862 BIOSIS
 DN PREV199800055862
 TI Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12.
 AU **Leonard, John P.** (1); Waldburger, Kristine E. (1); Schaub, Robert G. (1); Smith, Terence; Hewson, Adrian K.; Cuzner, M. Louis; **Goldman, Samuel J.** (1)
 CS (1) Genetics Inst. Preclinical Pharmacology, Andover, MA 01810 USA
 SO Critical Reviews in Immunology, (1997) Vol. 17, No. 5-6, pp. 545-553.
 ISSN: 1040-8401.
 DT General Review
 LA English

L14 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2001 ACS
 AN 1997:105274 CAPLUS
 DN 126:122472
 TI Peptide/protein suspended formulations
 IN Eckenhoff, James B. Di; Holladay, Leslie A.; **Leonard, John Joseph, Jr.**; Leung, Iris K. M.; Tao, Sally A.; Magruder, Judy A.; Carr, John P.; Wright, Jeremy
 PA Alza Corporation, USA; Eckenhoff, Bonnie, J.; Holladay, Leslie A.; Leonard, John Joseph, Jr.; Leung, Iris K., M.; Tao, Sally A.; Magruder,

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9640049	A1	19961219	WO 1996-US7377	19960522
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5904935	A	19990518	US 1995-475238	19950607
	CA 2220871	AA	19961219	CA 1996-2220871	19960522
	AU 9658694	A1	19961230	AU 1996-58694	19960522
	AU 706318	B2	19990617		
	EP 831773	A1	19980401	EP 1996-920358	19960522
	EP 831773	B1	19991201		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,				

FI	CN 1187119	A	19980708	CN 1996-194494	19960522
	JP 11506730	T2	19990615	JP 1996-500644	19960522
	AT 187062	E	19991215	AT 1996-920358	19960522
	ES 2139360	T3	20000201	ES 1996-920358	19960522
	FI 9704429	A	19971205	FI 1997-4429	19971205
	US 5972370	A	19991026	US 1999-238159	19990128

PRAI US 1995-475238 19950607
WO 1996-US7377 19960522

AB A stabilized, concd. non-aq. suspension formulations for peptides and proteins, suitable for use in an implantable device which delivers the formulation over an extended delivery period, comprises at least 5% by

wt.

drug (particle size 1-10 .mu.), a low-mol.-wt. polyol (e.g. polyethylene glycol) and a thickening agent (povidone or hydroxypropyl cellulose). Implants contg. 10% cytochrome c in a 50:50 PVP/PEG 400 carrier released the drug over 42 days into culture tubes filled with water.

L14 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 4

AN 1996:124298 BIOSIS

DN PREV199698696433

TI Adoptive transfer of experimental allergic encephalomyelitis after in vitro treatment with recombinant murine interleukin-12: Preferential expansion of **interferon-gamma**-producing cells and increased expression of macrophage-associated inducible nitric oxide synthase as immunomodulatory mechanisms.

AU Waldburger, Kristine E.; Hastings, Richard C.; Schaub, Robert G.;

Goldman, Samuel J.; Leonard, John P. (1)

CS (1) Genetics Inst., One Burt Road, Andover, MA 01810 USA

SO American Journal of Pathology, (1996) Vol. 148, No. 2, pp. 375-382.

ISSN: 0002-9440.

DT Article

LA English

AB In an adoptive transfer model of experimental allergic encephalomyelitis, stimulation of lymph node cells with proteolipid protein and recombinant murine interleukin (rmIL)-12 before cell transfer accelerated the onset and exacerbates clinical disease. In vitro stimulation with proteolipid protein in the presence of rmIL-12 was associated with an increase in **interferon-gamma**-producing cells and a decrease in IL-4-producing cells, indicating a preferential expansion of Th1 effector cells. This

was

supported by the finding that severe disease with rapid onset could be transferred with as few as 10 times 10⁻⁶ rmIL-12-stimulated lymph node

cells. Immunohistochemical analysis confirmed that the accelerated onset of disease after in vitro stimulation with rmIL-2 coincided with an acute inflammatory response in the central nervous system. At peak disease,

both

control and rmIL-12 treatment groups exhibited extensive cellular infiltration with characteristic perivascular cuffing. No notable differences in either the cellular composition or cytokine expression within the lesions were seen between groups. However, the frequency of macrophages that stained positively for inducible nitric oxide synthase was increased in animals challenged with rmIL-12-treated lymph node

cells.

The results suggest that, in addition to promoting the preferential expansion of **interferon**-gamma-producing cells by rmIL-12 in vitro, secondary in vivo effects leading to macrophage activation and inducible nitric oxide synthase expression may contribute to the severe and protracted course of central nervous system inflammation in this model.

L14 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2001 ACS

AN 1997:109341 CAPLUS

DN 126:170025

TI Regulation of experimental autoimmune encephalomyelitis by interleukin-12

AU Leonard, John P.; Waldburger, Kristine E.; Goldman, Samuel J.

CS Preclinical Biology Genetics Institute, Andover, MA, 01810, USA

SO Ann. N. Y. Acad. Sci. (1996), 795(Interleukin 12), 216-226

CODEN: ANYAA9; ISSN: 0077-8923

PB New York Academy of Sciences

DT Journal; General Review

LA English

AB A review with 28 refs. The authors evaluated the role of recombinant murine interleukin-12 (rmIL-12) on the course of exptl. autoimmune encephalomyelitis (EAE) following the adoptive transfer of the encephalitogenic protein-stimulated lymph node cells to naive SJL/J mice. The results demonstrate a central role for interleukin-12 in regulating the autoimmune response in this murine model of EAE. Furthermore, the available data suggest that the mechanism of action of rmIL-12 is independent of secondary **interferon**-gamma secretion.

L14 ANSWER 14 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1995:187042 BIOSIS

DN PREV199598201342

TI Combination interleukin-12 and bacille Calmette-Guerin immune therapy of bladder carcinoma in mice.

AU Hunter-Mayor, Sharon E.; O'Donnell, Michael; Szilvasi, Akos; Leonard, John; Clinton, Steven K.

CS Genetics Inst., Cambridge, MA 02140 USA

SO Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 480.

Meeting Info.: Eighty-sixth Annual Meeting of the American Association

for

Cancer Research Toronto, Ontario, Canada March 18-22, 1995

ISSN: 0197-016X.

DT Conference

LA English

L14 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 5

AN 1996:74926 BIOSIS

DN PREV199698647061

TI Structural characterization of the recombinant P40 heavy chain subunit monomer and homodimer of murine IL-12.

AU Nickbarg, Elliott B. (1); Vath, James E.; Pittman, Debra D.; Leonard, John E.; Waldburger, Kristine E.; Bond, Michael D.

CS (1) Genetics Inst. Inc., 87 Cambridgepark Drive, Cambridge, MA 02140 USA

SO Bioorganic Chemistry, (1995) Vol. 23, No. 4, pp. 380-396.

DT Article

LA English

AB Interleukin-12 (IL-12) is a heterodimeric cytokine that consists of two structurally unrelated subunits, P35 and P40. However, when expressed alone in Chinese hamster ovary (CHO) cells, murine P40 showed two species of different molecular weights under nonreducing conditions, a monomeric form of 45 kDa and a homodimer of gt 97 kDa. Under reducing conditions

the

two forms migrated as an identical array of species of 40-45 kDa. The monomer was separated from the homodimer under nonreducing conditions by heparin affinity chromatography and the disulfide bond structures of both species were determined by peptide mapping. Edman sequencing, and mass spectrometry. The peptide maps of the two species were identical except for a single peak that changed retention time. Sequencing showed that

this

peak contained two peptides of identical sequences in both maps. Mass spectrometric analysis of the peak from the gt 97-kDa species revealed an ion of double the expected mass, thus indicating that the peptide pair

had

dimerized. Mass analysis of the peak from the 40- to 45-kDa species

showed

that the peptide pair contained a mass difference that corresponded to that of an extra cysteine and which disappeared upon reduction. Amino

acid

analysis confirmed that the monomeric form of rmP40 is modified by a reducible cysteine. Structural analysis of the remainder of the cysteine-containing peaks showed that both species of rmP40 contained the same set of intramolecular disulfide bonds. The murine P40 homodimer arises from formation of a single intermolecular disulfide bond at Cys-175. In the monomeric P40, however, this cysteine is capped by an additional cysteine. Purified rmP40 monomer and homodimer inhibited the IL-12-dependent induction of *interferon*-gamma, but neither appeared capable of inducing IL-12-like biological activity.

L14 ANSWER 16 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6

AN 1994:393050 BIOSIS

DN PREV199497406050

TI Tyrosine phosphorylation of JAK-TYK kinases in malignant plasma cell lines

growth-stimulated by interleukins 6 and 11.

AU Berger, Lloyd C.; Hawley, Teresa S.; Lust, John A.; **Goldman, Samuel J.**; Hawley, Robert G. (1)

CS (1) Div. Cancer Res., Sunnybrook Health Sci. Cent., Dep. Med. Biophysics, Univ. Toronto, Toronto, ON M4N 3M5 Canada

SO Biochemical and Biophysical Research Communications, (1994) Vol. 202, No. 1, pp. 596-605.

ISSN: 0006-291X.

DT Article

LA English

AB The pleiotropic cytokine interleukin (IL)-6 is a major growth factor for murine plasmacytomas/hybridomas and human myeloma cells. Here we report that IL-6 stimulated different patterns of tyrosine phosphorylation of JAK-TYK kinases in IL-6-responsive murine (B9E and T10D) and human

(ANBL-6

and OCI-My4) plasma cell tumor lines. Interestingly, the Stat91 transcription factor essential for *interferon* signaling mediated by JAK-TYK kinases was significantly tyrosine phosphorylated in response to IL-6 in ANBL-6 cells but not in the other cell lines. We further show that IL-11, a cytokine that signals via the gp130 subunit of the IL-6 receptor, induced similar profiles of JAK-TYK tyrosine phosphorylation as IL-6 in B9E and T10D cells. These results suggest that functionally redundant JAK-TYK kinase cascades triggered through gp130 are involved in the growth regulation of plasma cell neoplasms.

L14 ANSWER 17 OF 17 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1993:343704 BIOSIS
 DN PREV199396040704
 TI Resolution of cutaneous leishmaniasis: Interleukin 12 initiates a protective T helper type 1 immune response.
 AU Sypek, Joseph P. (1); Chung, Charles L.; Mayor, Sharon E. H.; Subramanyam, Janaki M.; Goldman, Samuel L.; Sieburth, Derek S.; Wolf, Stanley F.; Schaub, Robert G.
 CS (1) Dep. Preclin. Biol., Genetics Inst. Inc., 87 Cambridge Park Dr., Cambridge, MA 02140 USA
 SO Journal of Experimental Medicine, (1993) Vol. 177, No. 6, pp. 1797-1802. ISSN: 0022-1007.
 DT Article
 LA English
 AB Resistance to Leishmania major in mice is associated with the appearance of distinct T helper type 1 (Th1) and Th2 subsets. T cells from lymph nodes draining cutaneous lesions of resistant mice are primarily **interferon** γ (IFN- γ)-producing Th1 cells. In contrast, T cells from susceptible mice are principally Th2 cells that generate interleukin 4 (IL-4). Although existing evidence is supportive of a role for IFN- γ in the generation of Th1 cells, additional factors may be required for a protective response to be maintained. A potential candidate is IL-12, a heterodimeric cytokine produced by monocytes and B cells that has multiple effects on T and natural killer cell function, including inducing IFN- γ production. Using an experimental leishmanial model we have observed that daily intraperitoneal administration at the time of parasite challenge of either 0.33 μ -g IL-12 (a consecutive 5 d/wk for 5 wk) or 1.0 μ -g IL-12 per mouse (only a consecutive 5 d) caused a \geq 75% reduction in parasite burden at the site of infection, in highly susceptible BALB/c mice. Delay of treatment by 1 wk had less of a protective effect. Concomitant with these protective effects was an increase in IFN- γ and a decrease in IL-4 production, as measured by enzyme-linked immunosorbent assay of supernatants generated from popliteal lymph node cells stimulated with leishmanial antigen in vitro. The reduction in parasite numbers induced by IL-12 therapy was still apparent at 10 wk postinfection. In addition, we observed that the administration of a rabbit anti-recombinant murine IL-12 polyclonal antibody (200 μ -g i.p. every other day for 25 d) at the time of infection to resistant C57Bl/6 mice exacerbated disease. These effects were accompanied by a shift in IFN- γ production in vitro by antigen-stimulated lymph node cells indicative of a Th2-like response. These findings suggest that IL-12 has an important role in initiating a Th1 response and protective immunity.

=> s il-12 and antagonist?

6 FILES SEARCHED...

L15 1014 IL-12 AND ANTAGONIST?

=> s l15 and multiple sclerosis

L16 84 L15 AND MULTIPLE SCLEROSIS

=> dup rem l16

PROCESSING COMPLETED FOR L16
L17 80 DUP REM L16 (4 DUPLICATES REMOVED)

=> s 117 and antibod?

6 FILES SEARCHED...
L18 64 L17 AND ANTIBOD?

=> s 118 and il-12 (10a) antibod?

8 FILES SEARCHED...
L19 18 L18 AND IL-12 (10A) ANTIBOD?

=> d bib ab 1-18

L19 ANSWER 1 OF 18 USPATFULL
AN 2000:138395 USPATFULL
TI Treatment of T-helper cell type 2-mediated immune disease by retinoid

IN antagonists
Bollag, Werner, Basel, Switzerland
Klaus, Michael, Weil am Rhein, Germany, Federal Republic of

PA Panina-Bordignon, Paola, Milan, Italy
PI Sinigaglia, Francesco, Milan, Italy
AI Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PRAI US 6133309 20001017
DT US 1998-189189 19981110 (9)
EXNAM EP 1997-119776 19971112

LREP Utility
CLMN Primary Examiner: Travers, Russell
ECL Johnston, George W.; Epstein, William H.; Parise, John P.

DRWN Number of Claims: 37
LN.CNT Exemplary Claim: 1
780 No Drawings

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Retinoids with retinoid receptor **antagonistic** activity,
pharmaceutically acceptable salts and pharmaceutically acceptable
hydrolyzable esters thereof, have been found efficacious in treating
T-helper cell type 2 (Th2)-mediated immune diseases, such as
immunoglobulin E (IgE)-mediated allergic diseases.

L19 ANSWER 2 OF 18 USPATFULL

AN 2000:50737 USPATFULL
TI Methods and compositions for modulating responsiveness to
corticosteroids

IN Sekut, Les, Westborough, MA, United States
Carter, Adam, Newburyport, MA, United States
Ghayur, Tariq, Grafton, MA, United States
Banerjee, Subhashis, Shrewsbury, MA, United States
Tracey, Daniel E., Harvard, MA, United States

PA BASF Aktiengesellschaft, Rheinland Pfalz, Germany, Federal Republic of
(non-U.S. corporation)

PI US 6054487 20000425
AI US 1997-820692 19970318 (8)
DT Utility

EXNAM Primary Examiner: Jarvis, William R. A.

LREP Lahive & Cockfield, LLP

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN 3 Drawing Figure(s); 3 Drawing Page(s)

LN.CNT 2404

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method for modulating responsiveness to corticosteroids in a subject
are

provided. In the method of the invention, an agent which antagonizes a factor that regulates production of IFN- γ in the subject is administered to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject. In one embodiment, the agent is an interferon- γ inducing factor (IGIF) **antagonist**. In another embodiment, the agent is an interleukin-12 (IL-12) **antagonist**. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-IL-12 monoclonal **antibody**. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunological diseases and disorders. Pharmaceutical compositions comprising an agent which antagonizes a factor that regulates production of IFN- γ in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred composition comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L19 ANSWER 3 OF 18 USPATFULL

AN 2000:4618 USPATFULL
 TI Protein kinase homologs
 IN Bandman, Olga, Mountain View, CA, United States
 Yang, Y. Tom, San Jose, CA, United States
 Hillman, Jennifer L., Mountain View, CA, United States
 Yue, Henry, Sunnyvale, CA, United States
 Guegler, Karl J., Menlo Park, CA, United States
 Corley, Neil C., Mountain View, CA, United States
 Gorgone, Gina A., Boulder Creek, CA, United States
 Azimzai, Yalda, Union City, CA, United States
 Lu, Dyung Aina M., San Jose, CA, United States
 PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
 PI US 6013455 20000111
 AI US 1998-173581 19981015 (9)
 DT Utility
 EXNAM Primary Examiner: Achutamurthy, Ponnathapu; Assistant Examiner: Moshipouri, M.
 LREP Muenzen, Colette C. Incyte Pharmaceuticals, Inc.
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 3258
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The invention provides human protein kinase homologs (PKH) and polynucleotides which identify and encode PKH. The invention also provides expression vectors, host cells, **antibodies**, agonists, and **antagonists**. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of PKH.

L19 ANSWER 4 OF 18 USPATFULL

AN 1999:163661 USPATFULL
 TI Interferon stimulating protein and uses thereof
 IN Hilbert, David M., Bethesda, MD, United States
 Bednarik, Daniel P., Columbia, MD, United States
 Nardelli, Bernadetta, Gaithersburg, MD, United States
 Murphy, Marianne, Richmond, United Kingdom
 Parmelee, David, Rockville, MD, United States
 Gronowski, Ann, Ballwin, MO, United States
 Schreiber, Robert, St. Louis, MO, United States

FA Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)
Washington University, St. Louis, MO, United States (U.S. corporation)
PI US 6001806 19991214
AI US 1998-105039 19980626 (9)
PRAI US 1997-51053 19970627 (60)
DT Utility
EXNAM Primary Examiner: MacMillan, Keith D.; Assistant Examiner: Wessendorf, T. D.
LREP Hoover, Kenley K.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 3165

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the use of the baculovirus glycoprotein, Interferon Stimulating Protein (ISP) (also known as gp67, gp64 EFP, or gp64), or the gene sequence encoding ISP, to stimulate production of interferon, such as for immunotherapy, anti-viral, anti-cancer, anti-bacterial, or anti-parasitic therapy. This invention also relates to novel mutant forms of ISP that show enhanced biological (i.e., anti-viral) activity, increased stability, higher yield or better solubility.

L19 ANSWER 5 OF 18 USPATFULL

AN 1999:146562 USPATFULL

TI Compositions and methods for decreasing IGIF and IFN-.gamma. production by administering an ICE inhibitor

IN Su, Michael, Newton, MA, United States

Gu, Yong, Brookline, MA, United States

Livingston, David J., Newtonville, MA, United States

PA Vertex Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

PI US 5985863 19991116

AI US 1996-712878 19960912 (8)

DT Utility

EXNAM Primary Examiner: Jordan, Kimberly

LREP Fish & Neave; Haley, Jr., James F.; Dixon, Lisa A.

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 35 Drawing Page(s)

LN.CNT 1766

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and pharmaceutical compositions

for decreasing the production of interferon-gamma inducing factor (IGIF). The invention also relates to methods and pharmaceutical compositions for decreasing the production of interferon-gamma (IFN-.gamma.). The compositions comprise a therapeutically effective amount of a compound which inhibits interleukin-1.beta. converting enzyme (ICE) and a pharmaceutically acceptable carrier. The methods comprise the step of administering the above compositions to a subject. The present invention also relates to methods for treating or reducing the advancement, severity or effects of an IGIF- or

IFN-.gamma.-mediated

inflammatory, infectious or autoimmune condition.

L19 ANSWER 6 OF 18 USPATFULL

AN 1999:110204 USPATFULL

TI Human growth-related CDC10 homolog

IN Hillman, Jennifer L., Mountain View, CA, United States

Yue, Henry, Sunnyvale, CA, United States

Guegler, Karl J., Menlo Park, CA, United States

Kaser, Matthew R., Castro Valley, CA, United States

Mathur, Preeti, Fremont, CA, United States

corporation)
 PI US 5952214 19990914
 AI US 1998-205681 19981204 (9)
 RLI Division of Ser. No. US 1997-978182, filed on 25 Nov 1997, now
 patented,
 Pat. No. US 5849556
 DT Utility
 EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Mayhew, Bradley
 S.
 LREP Incyte Pharmaceuticals, Inc; Mohan-Peterson, Sheela
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
 LN.CNT 2445
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The invention provides a human growth-related CDC10 homolog (GR-SEP)
 and
 polynucleotides which identify and encode GR-SEP. The invention also
 provides expression vectors, host cells, agonists, **antibodies**
 and **antagonists**. The invention also provides methods for
 treating and preventing disorders associated with expression of GR-SEP.

L19 ANSWER 7 OF 18 USPATFULL
 AN 1999:89052 USPATFULL
 TI Human nucleolin-like protein
 IN Bandman, Olga, Mountain View, CA, United States
 Yue, Henry, Sunnyvale, CA, United States
 Corley, Neil C., Mountain View, CA, United States
 Shah, Purvi, Sunnyvale, CA, United States
 PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S.
 corporation)
 PI US 5932475 19990803
 AI US 1997-990114 19971212 (8)
 DT Utility
 EXNAM Primary Examiner: Huff, Sheela
 LREP Incyte Pharmaceuticals, Inc.
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
 LN.CNT 2215
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The invention provides a human nucleolin-like protein (HNLP) and
 polynucleotides which identify and encode HNLP. The invention also
 provides expression vectors, host cells, **antibodies**, agonists,
 and **antagonists**. The invention also provides methods for
 treating or preventing disorders associated with expression of HNLP.

L19 ANSWER 8 OF 18 USPATFULL
 AN 1999:75759 USPATFULL
 TI Low affinity human IL-12 beta2 receptor
 IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
 Presky, David Howard, Glen Ridge, NJ, United States
 PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
 PI US 5919903 19990706
 AI US 1997-914520 19970819 (8)
 RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996
 PRAI US 1995-1701 19950801 (60)
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 1531

CAS INDEXING IS AVAILABLE FOR THIS PATENT

AB A recombinant human IL-12 receptor complex produced on the surface of a non-human mammalian cell and free from other human proteins, the complex comprising the beta2 receptor protein complexed with a beta2 receptor protein, which complex is capable of binding to human IL-12 with high affinity. A recombinant human IL-12 beta2 receptor protein produced on the surface of a non-human mammalian cell, free from other human proteins, in its active form. In addition, a non-human mammalian cell having expressed on

its surface the recombinant human IL-12 beta2 receptor protein or the recombinant human IL-12 receptor complex, which cell proliferates in the presence of human IL-12. A non-human mammalian cell having the human IL-12 beta2 receptor protein or the complex expressed on its surface and which proliferates in response to human IL-12 is useful for determining whether a given compound inhibits biological activity of human IL-12 or is an IL-12 agonist.

L19 ANSWER 9 OF 18 USPATFULL

AN 1998:161997 USPATFULL

TI **Antibody** to interleukin-12 receptor

IN Gately, Maurice Kent, Pine Brook, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

Wu, Chang-you, Belleville, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5853721 19981229

AI US 1995-381059 19950131 (8)

DT Utility

EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin

LREP Johnston, George W.; Tramaloni, Dennis P.; Kass, Alan P.

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 33 Drawing Figure(s); 22 Drawing Page(s)

LN.CNT 1418

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel **antibody** against the IL-12 receptor and a novel combination of antibodies against the IL-12 receptor. The novel anti-IL-12 receptor antibody, designated as 2B10, provided in accordance with the present invention binds to the human IL-12 receptor but which is not capable of inhibiting the binding of human IL-12 to the high affinity human IL-12 receptor and is not capable of neutralizing human IL-12 bioactivity by binding to human IL-12 receptor.

L19 ANSWER 10 OF 18 USPATFULL

AN 1998:160106 USPATFULL

TI **Antibodies** to receptors for human interleukin-12

IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5852176 19981222

AI US 1997-915495 19970820 (8)

RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996

PRAI US 1995-1701 19950801 (60)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1381

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antibodies** to human IL-12 beta 2 receptor protein or an IL-12 receptor complex, the complex comprising the beta2 receptor protein complexed with a beta2 receptor protein, which complex is capable of binding to human IL-12 with high affinity.

L19 ANSWER 11 OF 18 USPATFULL

AN 1998:157165 USPATFULL

TI Human growth-related CDC10 homolog

IN Hillman, Jennifer L., Mountain View, CA, United States

Yue, Henry, Sunnyvale, CA, United States

Guegler, Karl J., Menlo Park, CA, United States

Kaser, Matthew R., Castro Valley, CA, United States

Mathur, Preeti, Fremont, CA, United States

PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

PI US 5849556 19981215

AI US 1997-978182 19971125 (8)

DT Utility

EXNAM Primary Examiner: Hendricks, Keith D.; Assistant Examiner: Mayhew, Bradley S.

LREP Incyte Pharmaceuticals, Inc.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 2398

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human growth-related CDC10 homolog (GR-SEP) and

polynucleotides which identify and encode GR-SEP. The invention also provides expression vectors, host cells, agonists, **antibodies** and **antagonists**. The invention also provides methods for treating and preventing disorders associated with expression of GR-SEP.

L19 ANSWER 12 OF 18 USPATFULL

AN 1998:147252 USPATFULL

TI DNA encoding receptors for the beta-2 chain of human IL-12

IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5840530 19981124

AI US 1996-685118 19960723 (8)

PRAI US 1995-1701 19950801 (60)

US 1996-18674 19960530 (60)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1424

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A recombinant human IL-12 beta2 receptor protein produced on the surface of a non-human mammalian cell, free from other human proteins, in its active form. In addition, a non-human mammalian cell having expressed on its surface the recombinant human IL-12 beta2 receptor protein, which cell proliferates in the presence of human IL-12. A non-human mammalian cell having the human IL-12 beta2 receptor protein on its surface and which proliferates in response to human IL-12 is useful for determining whether a given compound inhibits biological activity of human IL-12 or is an IL-12 agonist.

L19 ANSWER 13 OF 18 USPATFULL
AN 1998:135151 USPATFULL
TI Human receptor for interleukin-12
IN Chua, Anne On, Wayne, NJ, United States
Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5831007 19981103
AI US 1995-419652 19950411 (8)
RLI Division of Ser. No. US 1994-248532, filed on 31 May 1994, now patented,
Pat. No. US 5536657 which is a continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John
LREP Johnston, George W.; Epstein, William H.; Bucholz, Briana C.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 35 Drawing Figure(s); 26 Drawing Page(s)
LN.CNT 1937

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to substantially pure Interleukin-12 receptor cDNAs and protein and uses therefore. The Interleukin-12 receptor is shown to be a member of the cytokine receptor superfamily and has a high
homology to human gp130.

L19 ANSWER 14 OF 18 USPATFULL
AN 97:64091 USPATFULL
TI P-40 homodimer of interleukin-12
IN Gately, Maurice Kent, Pine Brook, NJ, United States
Hakimi, John, Scarsdale, NY, United States
Ling, Ping, Nutley, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5650492 19970722
AI US 1995-424682 19950418 (8)
RLI Continuation of Ser. No. US 1993-87832, filed on 2 Jul 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Mertz, Prema
LREP Johnston, George W.; Tramaloni, Dennis P.; Kass, Alan P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 854

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Analysis of the culture media of p40-transfected COS cells indicated the
presence of 40 kDa monomers and 80 kDa disulfide-linked homodimers. Examination of partially purified p40 recombinant proteins demonstrated that only the homodimer but not the monomer binds to the IL-
12 receptor. Partially purified 80 kDa homodimer inhibited
[.sup.125 I]IL-12 binding to PHA-activated human lymphoblasts with an IC.sub.50 of 80 ng/ml, which is similar to the IC.sub.50 value (20 ng/ml) for the human IL-12 heterodimer. Although neither the 40 kDa monomer nor the 80 kDa dimer could stimulate human PHA-blast proliferation, the 80 kDa dimer inhibited IL-12-induced proliferation in a dose-dependent manner with an IC.sub.50 of 1 .mu.g/ml. The IL-
12 p40 subunit contains the essential epitopes for receptor binding, but they are only active when p40 is covalently associated with
a second protein such as p35 or p40. When p40 is associated with the p35 subunit, the heterodimer acts as an agonist mediating biologic activity.

When p40 associates with itself, the homodimer behaves as an antagonist.

L19 ANSWER 15 OF 18 USPATFULL
AN 96:63048 USPATFULL
TI Recombinant DNA encoding human receptor for interleukin-12
IN Chua, Anne O., Wayne, NJ, United States
Gubler, Ulrich A., Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5536657 19960716
AI US 1994-248532 19940531 (8)
RLI Continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John
LREP Gould, George M.; Johnston, George W.; Kass, Alan P.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 34 Drawing Figure(s); 25 Drawing Page(s)
LN.CNT 1755
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to substantially pure Interleukin-12 receptor cDNAs and protein and uses therefore. The Interleukin-12 receptor is shown to be a member of the cytokine receptor superfamily and has a high homology to human gp130.

L19 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2001 ACS
AN 2000:688272 CAPLUS
DN 133:280563
TI Human **antibodies** that bind human IL-12 and methods for producing
IN Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela;
Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara;
Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L.
PA Basf A.-G., Germany; Genetics Institute Inc.; et al.
SO PCT Int. Appl., 377 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056772	A1	20000928	WO 2000-US7946	20000324
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRAI US 1999-126603 19990325
AB Human **antibodies**, preferably recombinant human **antibodies**, that specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred **antibodies** have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo. An **antibody** of the invention can be a full-length **antibody** or an antigen-binding portion thereof. The **antibodies**, or

antibody portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant

human

antibodies of the invention, and methods of synthesizing the recombinant human **antibodies**, are also encompassed by the invention.

RE.CNT 7

RE

- (2) Carter, R; HYBRIDOMA 1997, V16(4), P363 CAPLUS
 - (3) Genentech Inc; WO 9404679 A 1994 CAPLUS
 - (4) Genetics Inst; WO 9524918 A 1995 CAPLUS
 - (5) Irving, R; IMMUNOTECHNOLOGY 1996, V2(2), P127 CAPLUS
 - (6) Pini, A; JOURNAL OF IMMUNOLOGICAL METHODS 1997, V206(1-2), P171 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2001 ACS

AN 1999:487326 CAPLUS

DN 131:129052

TI **Antibodies** against human IL-12

IN Gately, Maurcie Kent; Presky, David Howard

PA F.Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9937682	A2	19990729	WO 1999-EP202	19990115
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9925177	A1	19990115	AU 1999-25177	19990115
	BR 9907743	A	20001017	BR 1999-7743	19990115
	EP 1049717	A2	20001108	EP 1999-904780	19990115
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,			

FI

PRAI US 1998-72333 19980123

WO 1999-EP202 19990115

AB The present invention relates to p75 heterodimer specific anti-human IL-12 **antibodies** that are characterized by a higher potency and greater efficacy in neutralizing human IL-12 bioactivity than known heterodimer specific IL-12 monoclonal **antibodies**. The heterodimer specific **antibodies** recognize one or more epitopes of the human IL-12 p75 heterodimer, but do not bind to the p40 subunit alone. The heterodimer specific IL-12 **antibodies** neutralize rhesus monkey IL-12 bioactivity with a potency similar to their potency for neutralizing human IL-12 bioactivity making them useful IL-12 **antagonists**. The monoclonal **antibodies** are therefore useful for diseases assocd. with aberrant Th1-type helper cell activity, e.g. **multiple sclerosis**, rheumatoid arthritis, autoimmune diabetes mellitus, Crohn's disease and ulcerative colitis.

L19 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2001 ACS

AN 1995:934127 CAPLUS

DN 123:337469

TI use of IL-12 and IL-12
antagonists in treatment of autoimmune diseases
IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				

SE JP 09510444 T2 19971021 JP 1995-524044 19950307

PRAI US 1994-212629 19940314
WO 1995-US2550 19950307

AB Autoimmune conditions such as **multiple sclerosis**, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering **IL-12** or an **IL-12 antagonist**. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with **IL-12** during restimulation, and alleviated by injection of a polyclonal **antibody** to **IL-12**.

=> d clm 8 9 10

L19 ANSWER 8 OF 18 USPATFULL

CLM What is claimed is:

1. A human interleukin-12 (**IL-12**) beta2 receptor protein which has the amino acid sequence SEQ ID NO:2, or a protein which has an amino acid sequence which is encoded by a nucleic acid sequence which hybridizes under stringent conditions to the nucleic acid sequence which encodes SEQ ID NO:2, which protein (a) has low binding affinity for human **IL-12**, and (b) when complexed with a human **IL-12** beta1 receptor protein forms a complex having high binding affinity to human **IL-12**, the protein being free from other human proteins.
2. The human **IL-12** beta2 receptor protein of claim 1, having SEQ ID NO:2.

L19 ANSWER 9 OF 18 USPATFULL

CLM What is claimed is:

1. A combination of human **IL-12** receptor specific

immunoglobulins which is capable of inhibiting the binding of human IL-12 to the high affinity human IL-12 receptor and is capable of neutralizing human IL-12 bioactivity by binding to the human IL-12 receptor, wherein each individual immunoglobulin is not individually capable of inhibiting the binding of human IL-12 to the high affinity human IL-12 receptor.

L19 ANSWER 10 OF 18 USPATFULL

CLM What is claimed is:

1. An **antibody** directed against a interleukin-12 (IL-12) beta2 receptor protein which protein (a) has low binding affinity for human IL-12, and (b) when complexed with a human IL-12 beta1 receptor protein forms a complex having high binding affinity to human IL-12.

=> d his

(FILE 'HOME' ENTERED AT 11:47:06 ON 08 MAR 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, USPATFULL, WPIDS, JAPIO, BIOTECHDS, AGRICOLA, CAPLUS' ENTERED AT 11:47:46 ON 08 MAR 2001

E LEONARD JOHN/AU
L1 421 S E3-E28
E GOLDMAN SAMUEL/AU
L2 73 S E3-E9
E OHARA RICHARD/AU
E OHARA RICHARD/AU
L3 1 S E1
L4 482 S L1 OR L2 OR L3
L5 21 S L4 AND IL-12
L6 15 DUP REM L5 (6 DUPLICATES REMOVED)
L7 8 S L4 AND MULTIPLE SCLEROSIS
L8 6 DUP REM L7 (2 DUPLICATES REMOVED)
L9 5 S L4 AND ANTAGONIST?
L10 4 DUP REM L9 (1 DUPLICATE REMOVED)
L11 3 S L4 AND RHEUMATOID ARTHRITIS
L12 3 DUP REM L11 (0 DUPLICATES REMOVED)
L13 24 S L4 AND INTERFERON
L14 17 DUP REM L13 (7 DUPLICATES REMOVED)
L15 1014 S IL-12 AND ANTAGONIST?
L16 84 S L15 AND MULTIPLE SCLEROSIS
L17 80 DUP REM L16 (4 DUPLICATES REMOVED)
L18 64 S L17 AND ANTIBOD?
L19 18 S L18 AND IL-12 (10A) ANTIBOD?

=> s l15 and rheumatoid arthritis

L20 104 L15 AND RHEUMATOID ARTHRITIS

=> s l20 and antibod?

L21 91 L20 AND ANTIBOD?

=> s l21 and il-12 (10a) antibod?

6 FILES SEARCHED...

L22 21 L21 AND IL-12 (10A) ANTIBOD?

=> dup rem l22

=> d bib ab 1-22

L23 ANSWER 1 OF 21 USPATFULL

AN 2000:138395 USPATFULL

TI Treatment of T-helper cell type 2-mediated immune disease by retinoid
antagonists

IN Bollag, Werner, Basel, Switzerland

Klaus, Michael, Weil am Rhein, Germany, Federal Republic of

Panina-Bordignon, Paola, Milan, Italy

Sinigaglia, Francesco, Milan, Italy

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 6133309 20001017

AI US 1998-189189 19981110 (9)

PRAI EP 1997-119776 19971112

DT Utility

EXNAM Primary Examiner: Travers, Russell

LREP Johnston, George W.; Epstein, William H.; Parise, John P.

CLMN Number of Claims: 37

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 780

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Retinoids with retinoid receptor **antagonistic** activity,
pharmaceutically acceptable salts and pharmaceutically acceptable
hydrolyzable esters thereof, have been found efficacious in treating
T-helper cell type 2 (Th2)-mediated immune diseases, such as
immunoglobulin E (IgE)-mediated allergic diseases.

L23 ANSWER 2 OF 21 USPATFULL

AN 2000:50737 USPATFULL

TI Methods and compositions for modulating responsiveness to
corticosteroids

IN Sekut, Les, Westborough, MA, United States

Carter, Adam, Newburyport, MA, United States

Ghayur, Tariq, Grafton, MA, United States

Banerjee, Subhashis, Shrewsbury, MA, United States

Tracey, Daniel E., Harvard, MA, United States

PA BASF Aktiengesellschaft, Rheinland Pfalz, Germany, Federal Republic of
(non-U.S. corporation)

PI US 6054487 20000425

AI US 1997-820692 19970318 (8)

DT Utility

EXNAM Primary Examiner: Jarvis, William R. A.

LREP Lahive & Cockfield, LLP

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN 3 Drawing Figure(s); 3 Drawing Page(s)

LN.CNT 2404

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Method for modulating responsiveness to corticosteroids in a subject
are

provided. In the method of the invention, an agent which antagonizes a
factor that regulates production of IFN-.gamma. in the subject is
administered to the subject in combination with a corticosteroid such
that responsiveness of the subject to the corticosteroid is modulated

as

compared to when a corticosteroid alone is administered to the subject.
In one embodiment, the agent is an interferon-.gamma. inducing factor
(IGIF) **antagonist**. In another embodiment, the agent is an
interleukin-12 (IL-12) **antagonist**. In a
preferred embodiment, the agent is an inhibitor of a caspase family

protease, preferably an ICE inhibitor. In another embodiment, the agent is an anti IL 10 monoclonal antibody. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunological diseases and disorders. Pharmaceutical compositions comprising an agent which antagonizes a factor that regulates production of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred composition comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L23 ANSWER 3 OF 21 USPATFULL

AN 2000:4618 USPATFULL

TI Protein kinase homologs

IN Bandman, Olga, Mountain View, CA, United States

Yang, Y. Tom, San Jose, CA, United States

Hillman, Jennifer L., Mountain View, CA, United States

Yue, Henry, Sunnyvale, CA, United States

Guegler, Karl J., Menlo Park, CA, United States

Corley, Neil C., Mountain View, CA, United States

Gorgone, Gina A., Boulder Creek, CA, United States

Azimzai, Yalda, Union City, CA, United States

Lu, Dyung Aina M., San Jose, CA, United States

PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

PI US 6013455 20000111

AI US 1998-173581 19981015 (9)

DT Utility

EXNAM Primary Examiner: Achutamurthy, Ponnathapu; Assistant Examiner: Moshipouri, M.

LREP Muenzen, Colette C. Incyte Pharmaceuticals, Inc.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3258

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides human protein kinase homologs (PKH) and polynucleotides which identify and encode PKH. The invention also provides expression vectors, host cells, **antibodies**, agonists, and **antagonists**. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of PKH.

L23 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2001 ACS

AN 2000:688272 CAPLUS

DN 133:280563

TI Human **antibodies** that bind human IL-12 and methods for producing

IN Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom,

Angela;

Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen,

Sara;

Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L.

PA Basf A.-G., Germany; Genetics Institute Inc.; et al.

SO PCT Int. Appl., 377 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.

KIND DATE

APPLICATION NO. DATE

PR 000 00000000 00000000 00000000 00000000
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
 CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
 ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
 LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
 SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
 ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-126603 19990325

AB Human **antibodies**, preferably recombinant human **antibodies**, that specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred **antibodies** have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo. An **antibody** of the invention can be a full-length **antibody** or an antigen-binding portion thereof. The **antibodies**, or **antibody** portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human **antibodies** of the invention, and methods of synthesizing the recombinant human **antibodies**, are also encompassed by the invention.

RE.CNT 7

RE

(2) Carter, R; HYBRIDOMA 1997, V16(4), P363 CAPLUS
 (3) Genentech Inc; WO 9404679 A 1994 CAPLUS
 (4) Genetics Inst; WO 9524918 A 1995 CAPLUS
 (5) Irving, R; IMMUNOTECHNOLOGY 1996, V2(2), P127 CAPLUS
 (6) Pini, A; JOURNAL OF IMMUNOLOGICAL METHODS 1997, V206(1-2), P171 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 21 USPATFULL

AN 1999:146562 USPATFULL

TI Compositions and methods for decreasing IGIF and IFN-.gamma. production by administering an ICE inhibitor

IN Su, Michael, Newton, MA, United States

Gu, Yong, Brookline, MA, United States

Livingston, David J., Newtonville, MA, United States

PA Vertex Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

PI US 5985863 19991116

AI US 1996-712878 19960912 (8)

DT Utility

EXNAM Primary Examiner: Jordan, Kimberly

LREP Fish & Neave; Haley, Jr., James F.; Dixon, Lisa A.

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 35 Drawing Page(s)

LN.CNT 1766

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and pharmaceutical compositions

for decreasing the production of interferon-gamma inducing factor (IGIF). The invention also relates to methods and pharmaceutical compositions for decreasing the production of interferon-gamma (IFN-.gamma.). The compositions comprise a therapeutically effective amount of a compound which inhibits interleukin-1.beta. converting enzyme (ICE) and a pharmaceutically acceptable carrier. The methods comprise the step of administering the above compositions to a subject. The present invention also relates to methods for treating or reducing the advancement, severity or effects of an IGIF- or

IFN-.gamma.-mediated

~~Inflammatory, infectious or autoimmune condition.~~

L23 ANSWER 6 OF 21 USPATFULL
AN 1999:128718 USPATFULL
TI Lymphocyte surface receptor that binds CAML, nucleic acids encoding the same and methods of use thereof
IN Bram, Richard J., Memphis, TN, United States
Von Bulow, Gotz, Memphis, TN, United States
PA St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)
PI US 5969102 19991019
AI US 1997-810572 19970303 (8)
DT Utility
EXNAM Primary Examiner: Saunders, David; Assistant Examiner: VanderVegt, F. Pierre
LREP Klauber & Jackson
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 3167
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel lymphocyte receptor protein, its DNA sequence, and its role in the calcium activation pathway is described. The protein, or genetically engineered constructs encoding it, are shown to increase lymphocyte response, and to identify ligands of the protein receptor.
Antibodies to the proteins of the invention are generated for diagnostic therapeutics. The protein and DNA can also be used for diagnostic purposes and for identifying agents for modulating the calcium induced activation pathway. A particular advantage of the present invention is that it provides lymphocyte activation of receptor found on all B cells, but only on a subset of T cells. The receptor can thus be targeted to specifically regulate B cell responses without affecting mature T cell activity. Such targeting specificity is always advantageous, particularly where an increase or decrease of **antibody** production is desired, e.g., during an infection (increase) or to avoid immune complex deposition complications (rheumatoid arthritis, glomerulonephritis, and other auto immune conditions).

L23 ANSWER 7 OF 21 USPATFULL
AN 1999:117656 USPATFULL
TI Human monoclonal **antibodies** against human cytokines and methods of making and using such **antibodies**
IN Garrone, Pierre, Lyons, France
Djossou, Odile, Francheville, France
Fossiez, Francois, Craponne, France
Banchereau, Jacques, Ecully, France
PA Schering Corporation, Kenilworth, NJ, United States (U.S. corporation)
PI US 5959085 19990928
WO 9514780 19950601
AI US 1996-646367 19960516 (8)
WO 1994-US13188 19941121
19960516 PCT 371 date
19960516 PCT 102(e) date
PRAI EP 1993-402846 19931123
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Davis, Minh-Tam
LREP Foulke, Cynthia L.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 1973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human monoclonal **antibodies** against a human cytokine (such as

~~antibodies are disclosed. Also disclosed are pharmaceutical~~
a human interleukin, e.g., human
compositions and methods employing the human monoclonal
antibodies and fragments, methods for screening for human
monoclonal **antibodies** against a human protein, methods for
producing a cDNA library enriched in DNA encoding V.sub.H and/or
V.sub.L
chains of a human monoclonal **antibody**, cell lines for making
the human monoclonal **antibodies**, and isolated DNA for making
the human monoclonal **antibodies** and fragments of the
invention.

L23 ANSWER 8 OF 21 USPATFULL

AN 1999:110204 USPATFULL

TI Human growth-related CDC10 homolog

IN Hillman, Jennifer L., Mountain View, CA, United States

Yue, Henry, Sunnyvale, CA, United States

Guegler, Karl J., Menlo Park, CA, United States

Kaser, Matthew R., Castro Valley, CA, United States

Mathur, Preeti, Fremont, CA, United States

PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S.
corporation)

PI US 5952214 19990914

AI US 1998-205681 19981204 (9)

RLI Division of Ser. No. US 1997-978182, filed on 25 Nov 1997, now
patented,

Pat. No. US 5849556

DT Utility

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Mayhew, Bradley
S.

LREP Incyte Pharmaceuticals, Inc; Mohan-Peterson, Sheela

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 2445

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human growth-related CDC10 homolog (GR-SEP)
and

polynucleotides which identify and encode GR-SEP. The invention also
provides expression vectors, host cells, agonists, **antibodies**
and **antagonists**. The invention also provides methods for
treating and preventing disorders associated with expression of GR-SEP.

L23 ANSWER 9 OF 21 USPATFULL

AN 1999:89052 USPATFULL

TI Human nucleolin-like protein

IN Bandman, Olga, Mountain View, CA, United States

Yue, Henry, Sunnyvale, CA, United States

Corley, Neil C., Mountain View, CA, United States

Shah, Purvi, Sunnyvale, CA, United States

PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S.
corporation)

PI US 5932475 19990803

AI US 1997-990114 19971212 (8)

DT Utility

EXNAM Primary Examiner: Huff, Sheela

LREP Incyte Pharmaceuticals, Inc.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 2215

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human nucleolin-like protein (HNLP) and
polynucleotides which identify and encode HNLP. The invention also
provides expression vectors, host cells, **antibodies**, agonists,

L23 ANSWER 10 OF 21 USPATFULL
AN 1999:75759 USPATFULL
TI Low affinity human IL-12 beta2 receptor
IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
Presky, David Howard, Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5919903 19990706
AI US 1997-914520 19970819 (8)
RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996
PRAI US 1995-1701 19950801 (60)
DT Utility
EXNAM Primary Examiner: Draper, Garnette D.
LREP Johnston, George W.; Rocha-Tramalon, Patricia S.; Silverman, Robert A.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1531

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A recombinant human IL-12 receptor complex produced
on the surface of a non-human mammalian cell and free from other human
proteins, the complex comprising the beta1 receptor protein complexed
with a beta2 receptor protein, which complex is capable of binding to
human IL-12 with high affinity. A recombinant human
IL-12 beta2 receptor protein produced on the surface
of a non-human mammalian cell, free from other human proteins, in its
active form. In addition, a non-human mammalian cell having expressed

on
its surface the recombinant human IL-12 beta2
receptor protein or the recombinant human IL-12
receptor complex, which cell proliferates in the presence of human
IL-12. A non-human mammalian cell having the human
IL-12 beta2 receptor protein or the complex expressed
on its surface and which proliferates in response to human IL-
12 is useful for determining whether a given compound inhibits
biological activity of human IL-12 or is an
IL-12 agonist.

L23 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2001 ACS
AN 1999:487326 CAPLUS
DN 131:129052
TI Antibodies against human IL-12
IN Gately, Maurcie Kent; Presky, David Howard
PA F.Hoffmann-La Roche A.-G., Switz.
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9937682	A2	19990729	WO 1999-EP202	19990115
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9925177	A1	19990115	AU 1999-25177	19990115
	BR 9907743	A	20001017	BR 1999-7743	19990115
	EP 1049717	A2	20001108	EP 1999-904780	19990115

F1

PRAI US 1998-72333 19980123

WO 1999-EP202 19990115

AB The present invention relates to p75 heterodimer specific anti-human **IL-12 antibodies** that are characterized by a higher potency and greater efficacy in neutralizing human **IL-12** bioactivity than known heterodimer specific **IL-12** monoclonal **antibodies**. The heterodimer specific **antibodies** recognize one or more epitopes of the human **IL-12** p75 heterodimer, but do not bind to the p40 subunit alone. The heterodimer specific **IL-12 antibodies** neutralize rhesus monkey **IL-12** bioactivity with a potency similar to their potency for neutralizing human **IL-12** bioactivity making them useful **IL-12 antagonists**. The monoclonal **antibodies** are therefore useful for diseases assocd. with aberrant Th1-type helper cell activity, e.g. multiple sclerosis, **rheumatoid arthritis**, autoimmune diabetes mellitus, Crohn's disease and ulcerative colitis.

L23 ANSWER 12 OF 21 MEDLINE

AN 1999354937 MEDLINE

DN 99354937

TI Anti-**IL-12** and anti-TNF **antibodies** synergistically suppress the progression of murine collagen-induced arthritis.

AU Butler D M; Malfait A M; Maini R N; Brennan F M; Feldmann M

CS Kennedy Institute of Rheumatology, London, GB.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jul) 29 (7) 2205-12.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199910

EW 19991002

AB The co-ordinate role of the Th1 cytokine **IL-12** and the proinflammatory cytokine TNF in arthritis was explored using the DBA/1 mouse model, collagen-induced arthritis (CIA). In this study, mice with established arthritis were treated with anti-**IL-12** and/or anti-TNF **antibodies** for 10 days from the onset of disease. Clinical assessment showed that the combined **antibody** treatment ameliorated disease severity to a greater extent than anti-TNF alone. Supporting these observations, histological analysis revealed that there was a reduced joint damage in the mice that received combined anti-**IL-12** and anti-TNF treatment, compared to the other treatment groups. Anti-**IL-12** had no statistically significant effect on the clinical outcome of disease. The combination of anti-**IL-12** and anti-TNF treatment was found to reduce collagen type II (CII)-specific lymph node cell IFN-gamma production and proliferation, as well as decrease the anti-CII IgG2a:IgG1 ratio more effectively than either treatment alone. When the **antibodies** were added to synovial cells from arthritic mice and bone marrow macrophages in vitro, anti-TNF diminished **IL-12** production, but anti-**IL-12** had no effect on TNF production. These data suggest that, through the partial regulation of **IL-12**, TNF modulates the immune response in arthritis, as well as the inflammatory response. The synergistic action of anti-TNF and anti-**IL-12** on CIA may provide a new therapeutic approach for treating **rheumatoid arthritis**.

L23 ANSWER 13 OF 21 USPATFULL

AN 1998:161997 USPATFULL

TI **Antibody** to interleukin-12 receptor

IN Gately, Maurice Kent, Pine Brook, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States
Wu, Chang-you, Belleville, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5853721 19981229
AI US 1995-381059 19950131 (8)
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin
LREP Johnston, George W.; Tramaloni, Dennis P.; Kass, Alan P.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 33 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 1418

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel **antibody** against the IL-12 receptor and a novel combination of antibodies against the IL-12 receptor. The novel anti-IL-12 receptor antibody, designated as 2B10, provided in accordance with the present invention binds to the human IL-12 receptor but which is not capable of inhibiting the binding of human IL-12 to the high affinity human IL-12 receptor and is not capable of neutralizing human IL-12 bioactivity by binding to human IL-12 receptor.

L23 ANSWER 14 OF 21 USPATFULL

AN 1998:160106 USPATFULL
TI **Antibodies** to receptors for human interleukin-12
IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
Presky, David Howard, Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5852176 19981222
AI US 1997-915495 19970820 (8)
RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996
PRAI US 1995-1701 19950801 (60)
DT Utility
EXNAM Primary Examiner: Draper, Garnette D.
LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1381

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antibodies** to human IL-12 beta 2 receptor protein or an IL-12 receptor complex, the complex comprising the beta1 receptor protein complexed with a beta2 receptor protein, which complex is capable of binding to human IL-12 with high affinity.

L23 ANSWER 15 OF 21 USPATFULL

AN 1998:157165 USPATFULL
TI Human growth-related CDC10 homolog
IN Hillman, Jennifer L., Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
Kaser, Matthew R., Castro Valley, CA, United States
Mathur, Preete, Fremont, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5849556 19981215
AI US 1997-978182 19971125 (8)
DT Utility
EXNAM Primary Examiner: Hendricks, Keith D.; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 10

ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2398

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a human growth-related CDC10 homolog (GR-SEP)
and

polynucleotides which identify and encode GR-SEP. The invention also
provides expression vectors, host cells, agonists, **antibodies**
and **antagonists**. The invention also provides methods for
treating and preventing disorders associated with expression of GR-SEP.

L23 ANSWER 16 OF 21 USPATFULL

AN 1998:147252 USPATFULL

TI DNA encoding receptors for the beta-2 chain of human IL-

12

IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5840530 19981124

AI US 1996-685118 19960723 (8)

PRAI US 1995-1701 19950801 (60)

US 1996-18674 19960530 (60)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1424

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A recombinant human IL-12 beta2 receptor protein
produced on the surface of a non-human mammalian cell, free from other
human proteins, in its active form. In addition, a non-human mammalian
cell having expressed on its surface the recombinant human IL-
12 beta2 receptor protein, which cell proliferates in the
presence of human IL-12. A non-human mammalian cell
having the human IL-12 beta2 receptor protein on its
surface and which proliferates in response to human IL-
12 is useful for determining whether a given compound inhibits
biological activity of human IL-12 or is an
IL-12 agonist.

L23 ANSWER 17 OF 21 USPATFULL

AN 1998:135151 USPATFULL

TI Human receptor for interleukin-12

IN Chua, Anne On, Wayne, NJ, United States

Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5831007 19981103

AI US 1995-419652 19950411 (8)

RLI Division of Ser. No. US 1994-248532, filed on 31 May 1994, now
patented,

Pat. No. US 5536657 which is a continuation-in-part of Ser. No. US
1993-94713, filed on 19 Jul 1993, now abandoned

DT Utility

EXNAM Primary Examiner: Ulm, John

LREP Johnston, George W.; Epstein, William H.; Bucholz, Briana C.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 35 Drawing Figure(s); 26 Drawing Page(s)

LN.CNT 1937

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to substantially pure Interleukin-12 receptor
cDNAs and protein and uses therefore. The Interleukin-12 receptor is
shown to be a member of the cytokine receptor superfamily and has a

high

L23 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2001 ACS
 AN 1998:640257 CAPLUS
 DN 129:255530
 TI Methods and compositions for modulating responsiveness to corticosteroids
 IN Sekut, Les; Carter, Adam; Chayur, Tariq; Banerjee, Subhashis; Tracey, Daniel E.
 PA Basf A.-G., Germany
 SO PCT Int. Appl., 112 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9841232	A2	19980924	WO 1998-US4916	19980312
	WO 9841232	A3	20001005		

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,

US
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US	6054487	A	20000425	US	1997-820692	19970318
AU	9867604	A1	19981012	AU	1998-67604	19980312
EP	998300	A1	20000510	EP	1998-912929	19980312

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,

FI	BR	9810409	A	20000822	BR	1998-10409	19980312
	NO	9904506	A	19991117	NO	1999-4506	19990917

PRAI US 1997-820692 19970318
 US 1998-16346 19980130
 WO 1998-US4916 19980312

AB Method for modulating responsiveness to corticosteroids in a subject are provided. In the method of the invention, an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in the subject is administered

to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when the corticosteroid is given alone. The method can be used to, for example, reverse steroid resistance or to increase steroid sensitivity, or to ameliorate the steroid rebound effect when subjects

are taken off corticosteroid treatment. In one embodiment, the agent is an IL-18 antagonist. In another embodiment, the agent is an interleukin-12 (IL-12) antagonist. In yet another embodiment, the agent is an NK cell antagonist. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-IL-12 monoclonal antibody. In yet another preferred embodiment, the agent is an anti-asialo-GM1 antibody or an NK1.1 antibody. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of

inflammatory and immunol. diseases and disorders. Pharmaceutical compns. comprising an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred compn. comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L23 ANSWER 10 OF 21 GADLUO 00000000 2001 ACC

AN 1998:351787 CAPLUS

DN 129:40158

TI Suppression of TNF.alpha. and IL-12 in therapy

IN Feldmann, Marc; Malfait, Anne-Marie Aline Michel; Butler, Debra Maree;
Brennan, Fionula Mary; Maini, Ravinder Nath

PA Kennedy Institute of Rheumatology, UK; Feldmann, Marc; Malfait,
Anne-Marie

Aline Michel; Butler, Debra Maree; Brennan, Fionula Mary; Maini, Ravinder
Nath

SO PCT Int. Appl., 66 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9822137	A1	19980528	WO 1997-GB3151	19971117
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	AU 9749599	A1	19980610	AU 1997-49599	19971117
	EP 936923	A1	19990825	EP 1997-912367	19971117
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			

PRAI US 1996-749979 19961115

WO 1997-GB3151 19971117

AB Methods for treating and/or preventing a TNF.alpha.-mediated disease in
an

individual are disclosed. Also disclosed are compns. comprising a TNF
antagonist and an **IL-12 antagonist**.

The TNF.alpha. **antagonist** is an **antibody** or a TNF
receptor/IgG fusion protein or thalidomide, and the **IL-12 antagonist** is an **antibody** or
phosphodiesterase inhibitor, e.g. pentoxifylline or rolipram.

TNF.alpha.-mediated diseases include **rheumatoid arthritis**, Crohn's disease, and acute and chronic immune diseases
assocd. with transplantation.

L23 ANSWER 20 OF 21 USPATFULL

AN 96:63048 USPATFULL

TI Recombinant DNA encoding human receptor for interleukin-12

IN Chua, Anne O., Wayne, NJ, United States

Gubler, Ulrich A., Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5536657 19960716

AI US 1994-248532 19940531 (8)

RLI Continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993,
now abandoned

DT Utility

EXNAM Primary Examiner: Ulm, John

LREP Gould, George M.; Johnston, George W.; Kass, Alan P.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 34 Drawing Figure(s); 25 Drawing Page(s)

LN.CNT 1755

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to substantially pure Interleukin-12 receptor
cDNAs and protein and uses therefore. The Interleukin-12 receptor is

nigh shown to be a member of the cytokine receptor superfamily and has a
homology to human gp130.

L23 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2001 ACS
AN 1995:934127 CAPLUS
DN 123:337469
TI Use of **IL-12** and **IL-12**
antagonists in treatment of autoimmune diseases
IN Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	JP 09510444	T2	19971021	JP 1995-524044	19950307
PRAI	US 1994-212629		19940314		
	WO 1995-US2550		19950307		
AB	Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis , autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering IL-12 or an IL-12 antagonist . Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12 .				

=> s 115 and interferon

L24 603 L15 AND INTERFERON

=> s 124 and antibod?

L25 281 L24 AND ANTIBOD?

=> s 125 and il-12 (10a) antibod?

5 FILES SEARCHED...

L26 88 L25 AND IL-12 (10A) ANTIBOD?

=> dup rem 126

PROCESSING COMPLETED FOR L26

=> d bib ab 40-63

L27 ANSWER 40 OF 63 MEDLINE
 AN 1998173244 MEDLINE
 DN 98173244
 TI Regulation of monocyte interleukin-12 production by acute alcohol: a role for inhibition by interleukin-10.
 AU Girouard L; Mandrekar P; Catalano D; Szabo G
 CS Department of Medicine, University of Massachusetts Medical Center, Worcester 01655, USA.
 NC AA08577 (NIAAA)
 SO ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (1998 Feb) 22 (1) 211-6.

Journal code: 35X. ISSN: 0145-6008.

CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199807
 EW 19980704
 AB Acute ethanol treatment results in decreased antigen presentation capacity
 (Th1-type immunity) and elevated interleukin IL-10 (Th2 cytokine) production in human monocytes. Monocytes can contribute to both Th1 (IL-12) and Th2 (IL-10) immune responses via production of IL-12 and IL-10, respectively. Thus, we tested the hypothesis that acute alcohol treatment might affect Th1/Th2 immune balance by altering monocyte production of IL-12 and IL-10. Neither acute ethanol treatment alone (25 to 100 mM) nor its combination with a bacterial challenge Staphylococcal enterotoxin B (SEB) induced IL-12 production in isolated blood monocytes. In contrast, the same physiological alcohol concentrations increased monocyte IL-10 levels, suggesting that ethanol can induce a dysbalance of monocyte-derived mediator production at the expense of Th1 cytokines. However, we found that monocyte activation with **interferon-gamma** (IFN-gamma) can prevent the preferential IL-10 induction by ethanol. IFN-gamma (100 units/ml) inhibited monocyte IL-10 production whether induced by 1 microg/ml of lipopolysaccharide (p < 0.01), 1 microg/ml of SEB (p < 0.02), or a combination of bacterial stimulation + ethanol (lipopolysaccharide: p < 0.01). Furthermore, decreased IL-10 was concomitant to an increase in IL-12 production in IFN-gamma-treated monocytes. Moreover, acute ethanol treatment augmented IL-12 production in IFN-gamma-treated monocytes in response to SEB stimulation (25 mM ethanol, p < 0.01; 100 mM ethanol, p < 0.01). Experiments with anti-IL-10 neutralizing **antibody** show that ethanol may prevent monocyte IL-12 induction via IL-10. These results suggest that inhibition of ethanol-induced IL-10 production by IFN-gamma treatment is permissive for IL-12 induction by alcohol stimulation in monocytes. Thus, our results imply that the presence or absence of IFN-gamma is critical in determining the effect of acute ethanol treatment on monocyte IL-12 versus IL-10 induction.

L27 ANSWER 41 OF 63 USPATFULL
 AN 97:64091 USPATFULL
 TI P-40 homodimer of interleukin-12
 IN Gately, Maurice Kent, Pine Brook, NJ, United States
 Hakimi, John, Scarsdale, NY, United States
 Ling, Ping, Nutley, NJ, United States
 PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
 PI US 5650492 19970722
 AI US 1995-424682 19950418 (8)

RLI Continuation of Ser. No. US 1993-87832, filed on 2 Jul 1993, now
abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Mertz, Prema
LREP Johnston, George W.; Tramaloni, Dennis P.; Kass, Alan P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 854

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Analysis of the culture media of p40-transfected COS cells indicated
the

presence of 40 kDa monomers and 80 kDa disulfide-linked homodimers.
Examination of partially purified p40 recombinant proteins demonstrated
that only the homodimer but not the monomer binds to the IL-
12 receptor. Partially purified 80 kDa homodimer inhibited
[.sup.125 I]IL-12 binding to PHA-activated human
lymphoblasts with an IC.sub.50 of 80 ng/ml, which is similar to the
IC.sub.50 value (20 ng/ml) for the human IL-12
heterodimer. Although neither the 40 kDa monomer nor the 80 kDa dimer
could stimulate human PHA-blast proliferation, the 80 kDa dimer
inhibited IL-12-induced proliferation in a
dose-dependent manner with an IC.sub.50 of 1 .mu.g/ml. The IL-
12 p40 subunit contains the essential epitopes for receptor
binding, but they are only active when p40 is covalently associated
with
a second protein such as p35 or p40. When p40 is associated with the
p35
subunit, the heterodimer acts as an agonist mediating biologic
activity.
When p40 associates with itself, the homodimer behaves as an
antagonist.

L27 ANSWER 42 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
AN 97245846 EMBASE
DN 1997245846

TI Lipopolysaccharide and monophosphoryl lipid A differentially regulate
interleukin-12, gamma interferon, and interleukin-10 mRNA
production in murine macrophages.

AU Salkowski C.A.; Detore G.R.; Vogel S.N.

CS S.N. Vogel, Microbiology/Immunology Department, USUHS, 4301 Jones Bridge
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SO Infection and Immunity, (1997) 65/8 (3239-3247).

Refs: 67

ISSN: 0019-9567 CODEN: INFIBR

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB Monophosphoryl lipid A (MPL) is a nontoxic derivative of the lipid A
region of lipopolysaccharide (LPS) that is being developed as both an
adjuvant and prophylactic drug for septic shock. We compared the ability
of LPS and MPL to induce interleukin-10 (IL-10), IL-12
p35, IL-12 p40, gamma interferon
(IFN-.gamma.), glucocorticoid receptor (GR), IL-1 receptor
antagonist (IL-1ra), and inducible nitric oxide synthase mRNA
expression in murine peritoneal macrophages. These genes were chosen for
their ability to positively or negatively regulate the host immune
response and thus for their potential involvement in MPL-induced
adjuvanticity or in its ability to protect against sepsis. LPS was a more
potent inducer of IL-12 p35, IL-12
p40; and IFN-.gamma. mRNA, as well as of IL-12
protein, than MPL. In contrast, MPL induced higher levels of IL-10 mRNA

than did LPS from 1 to 1,000 ng/ml. In general, MPL was not a more potent inducer of negative regulatory genes, since MPL and LPS induced similar levels of GR and IL-1ra mRNA. Addition of anti-IL-10 antibody to cultures increased the induction of MPL-induced IL-12 p35, IL-12 p40, and IFN- γ mRNA, suggesting that the enhanced production of IL-10 by MPL-stimulated macrophages contributes to decreased production of mRNA for IL-12 (p35 and p40) and IFN- γ . Conversely, the addition of exogenous IL-10 to LPS-treated macrophages reduced the mRNA expression of these cytokine genes. These studies suggest that enhanced production of IL-10 by MPL-stimulated macrophages may contribute to the reduced toxicity of MPL through its negative action on induction of cytokines shown to enhance endotoxicity.

L27 ANSWER 43 OF 63 MEDLINE

AN 1998056811 MEDLINE

DN 98056811

TI Immune complexes are potent inhibitors of interleukin-12 secretion by human monocytes.

AU Berger S; Chandra R; Ballo H; Hildenbrand R; Stutte H J

CS Senckenberg Center of Pathology, University of Frankfurt am Main, Germany.. S.Berger@em.uni-frankfurt.de

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Nov) 27 (11) 2994-3000.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199803

EW 19980302

AB We have studied the effect of immune complexes (IC) on interleukin (IL)-12 secretion by human monocytes in vitro. Two experimental models of IC were used. IC formed of tetanus toxoid and polyclonal anti-tetanus toxoid antiserum as well as heat-aggregated human serum IgG almost completely inhibited IL-12 (p70 and p40) secretion induced by interferon- γ and lipopolysaccharide in human blood-derived monocytes. Neutralizing anti-IL-10 antibodies plus indomethacin restored IL-12 secretion in the presence of IC to a high extent, indicating that IL-10 and prostaglandin (PG) partially mediate the IC-induced inhibition of IL-12 secretion. However, neutralization of tumor necrosis factor (TNF)- α by specific antibodies also incompletely restored IL-12 secretion. Indeed, monocytes secrete high levels of TNF- α upon stimulation by IC. We found that exogenously added TNF- α caused a profound inhibition of monocytic IL-12 secretion in the absence of IC, again mediated via the induction of IL-10 and PG. In summary, IC inhibit IL-12 secretion via TNF- α -induced IL-10 and PG synthesis. We conclude that IC, typically appearing in the course of chronic inflammatory processes, may influence the balance between Th1 and Th2 responses and may thus contribute to a deprivation of cell-mediated immune responses.

L27 ANSWER 44 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7

AN 97077516 EMBASE

DN 1997077516

TI Interferon- γ and interleukin-4 regulate T cell interleukin-12 responsiveness through the differential modulation of high-affinity interleukin-12 receptor expression.

AU Gollob J.A.; Kawasaki H.; Ritz J.

CS Dr. J.A. Gollob, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, United States

SO European Journal of Immunology, (1997) 27/3 (647-652).

Refs: 29

C1 Germany
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB **Interferon-.gamma.** (IFN-.gamma.) and interleukin-4 (IL-4) are mutually **antagonistic** cytokines that stimulate CD4+ T cells to develop into either Th1 or Th2 cells. One feature of Th2 differentiation in mice is the loss of **IL-12**-induced Jak2 and Stat4 activation, which is accompanied by the inability to produce IFN-.gamma. in response to **IL-12**. In this report, we show that freshly isolated human T cells activated with phytohemagglutinin (PHA) in the presence of IL-4 exhibit a greatly diminished response to **IL-12**, whereas the **IL-12** response of T cells activated with PHA plus IFN-.gamma. is enhanced. Radiolabeled **IL-12** binding studies demonstrate that the impairment of T cell **IL-12** responsiveness by IL-4 is associated with the down-regulation of high-affinity **IL-12** receptor expression. In contrast, the enhancement of **IL-12** responsiveness by IFN-.gamma. is associated with the upregulation of high affinity **IL-12** receptor expression. Through the use of a newly synthesized neutralizing **antibody** to the low-affinity **IL-12** receptor .beta. subunit (IL-12R.beta.), we show that neither IL-4 nor IFN-.gamma. affect the expression of IL-12R.beta., which we determine to be one of at least two low-affinity subunits required for high-affinity **IL-12** binding. These findings suggest that IL-4 and IFN-.gamma. exert opposite effects on T cell **IL-12** responsiveness by differentially modulating the expression of low-affinity **IL-12** receptor subunits that are distinct from IL-12R.beta. and required, together with IL-12R.beta., for high-affinity **IL-12** binding and **IL-12** responsiveness. This provides a basis for understanding the interplay between different cytokines at the level of cytokine receptor expression, and offers insight into one of the mechanisms governing Th1 and Th2 development.

L27 ANSWER 45 OF 63 MEDLINE

DUPLICATE 8

AN 97408449 MEDLINE

DN 97408449

TI Interleukin-13 effects on activated monocytes lead to novel cytokine secretion profiles intermediate between those induced by interleukin-10 and by **interferon-gamma**.

AU Minty A; Ferrara P; Caput D

CS Sanofi Recherche, Centre de Lab'ege, France..
adrian.minty@tllsl.elfsanof.fr

SO EUROPEAN CYTOKINE NETWORK, (1997 Jun) 8 (2) 189-201.
Journal code: A56. ISSN: 1148-5493.

CY France

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199712

EW 19971201

AB We have examined in detail the activities of IL-13 on monokine production in vitro and compared its effects with those of IL-10 and IFN-gamma.

IL-13

and IL-10 show qualitatively and quantitatively similar activities on cytokine production by monocytes when administered simultaneously with

LPS

i.e. inhibition of IL-1, IL-6 and TNF-alpha, up-regulation of IL1-ra. However when either LPS and IFN-gamma or fixed S. aureus Cowan (SAC) are used to activate monocytes, IL-10 is a much more potent inhibitor of TNF-alpha production than is IL-13. IL-10 is also an extremely potent inhibitor of **IL-12** (p70) production when given with

either SAC or LPS, while IL-13 has little effect. Indeed, IL-13 actually increases SAC-induced IL-12 production. When IL 10 is administered prior to the LPS stimulation, its modulation of cytokine production is drastically different. Production of IL-12, MCP-1, TNF-alpha and to a lesser extent IL-6 induced by LPS is now "primed", whereas that of IL-1, IL-8, and IL-10 is still inhibited. IL-10 does not show this "priming" effect, and is a dominant inhibitor of

IL-13.

The initial IL-13 priming effect is not however due to an inhibition of endogenous IL-10 production; nor is it due to inhibition of PGE2 production. The priming effect of IL-13 on IL-12 production is additive with that of IFN-gamma, and is partly independent of IFN-gamma. The earliest event in IL-13 priming so far noted is an increase in TNF-alpha mRNA production at 1-2 hours. IL-13 priming of IL-12 production can be completely abolished by anti-TNF-alpha antibodies suggesting that IL-13 may be priming via increased TNF-alpha expression, although merely substituting

TNF-alpha

for IL-13 does not reproduce the priming effect. IL-13 is thus a more subtle immune regulator than IL-10 or IFN-gamma. When administered with LPS or SAC, it dampens the resulting inflammatory response, though in a more selective way than IL-10. In contrast, when it is added before an inflammatory signal, it primes an immunostimulatory monokine secretion profile resembling that of IFN-gamma, but without the proinflammatory

IL-1

component. Early in response to an inflammatory stimulus, IL-13 may thus play an essentially anti-inflammatory role, switching to a primarily immunostimulatory role in the case of an ongoing infection.

L27 ANSWER 46 OF 63 MEDLINE

DUPLICATE 9

AN 97176660 MEDLINE

DN 97176660

TI Neospora caninum: role for immune cytokines in host immunity.

AU Khan I A; Schwartzman J D; Fonseka S; Kasper L H

CS Department of Medicine, Dartmouth Medical School, Hanover, New Hampshire 03755, USA.

SO EXPERIMENTAL PARASITOLOGY, (1997 Jan) 85 (1) 24-34.
Journal code: EQP. ISSN: 0014-4894.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199705

EW 19970501

AB Neospora caninum is a coccidial protozoan parasite that infects a large range of mammals including dogs, cats, mice, and cattle. Morphologically, N. caninum appears indistinguishable from Toxoplasma gondii, although

they

are genetically distinct. To date there have been no reported cases of this infection in humans, although nonhuman primates may be susceptible

to

infection. Inbred A/J mice develop no clinical and little histologic evidence of infection in spite of a high-dose inoculum of N. caninum. Splenocytes obtained from infected mice proliferate in vitro in response to both N. caninum and T. gondii-soluble antigen. A transient state of T cell hyporesponsiveness to parasite antigen and mitogen was observed at Day 7 p.i. This downregulatory response could be partially reversed by

the

addition of the nitric oxide antagonist LNMMA, but not antibody to IL-10. Mice infected with N. caninum produce significant quantities of IL-12 and IFN gamma, most evident shortly after infection. In vivo, antibody to IL-12 is able to neutralize immune resistance to the parasite. Moreover, in vivo depletion of IFN gamma with antibody renders the mice susceptible to infection. These observations suggest that N.

caninum induces a T cell immune response in the infected host that is at least partially mediated by IL-12 and IFN gamma.

L27 ANSWER 47 OF 63 USPATFULL
AN 96:63048 USPATFULL
TI Recombinant DNA encoding human receptor for interleukin-12
IN Chua, Anne O., Wayne, NJ, United States
Gubler, Ulrich A., Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5536657 19960716
AI US 1994-248532 19940531 (8)
RLI Continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Ulm, John
LREP Gould, George M.; Johnston, George W.; Kass, Alan P.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 34 Drawing Figure(s); 25 Drawing Page(s)
LN.CNT 1755

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to substantially pure Interleukin-12 receptor cDNAs and protein and uses therefore. The Interleukin-12 receptor is shown to be a member of the cytokine receptor superfamily and has a high homology to human gp130.

L27 ANSWER 48 OF 63 MEDLINE
AN 97131836 MEDLINE
DN 97131836
TI Effect of CD80 and CD86 blockade and anti-interleukin-12 treatment on mouse acute graft-versus-host disease.
AU Saito K; Yagita H; Hashimoto H; Okumura K; Azuma M
CS Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Dec) 26 (12) 3098-106.
Journal code: EN5. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199704
EW 19970402
AB We investigated the efficacy of a combination of anti-CD80 and CD86 (CD80 + 86) monoclonal **antibodies** (mAb), anti-interleukin (IL)-12 mAb, or both, for prophylaxis in a mouse acute graft-versus-host-disease (GVHD) model. The treatment with a combination of anti-CD80 + 86 mAb efficiently reduced the lethality of GVHD, whereas mAb against either CD80 or CD86 alone had an effect. A delay in lymphocyte reconstitution and GVHD-associated histological changes in organs was observed at 30 days post-bone marrow transplantation (BMT) even in the anti-CD80 + 86 mAb-treated mice, although these manifestations were resolved by 100 days. In vitro, host alloantigen-specific T cell proliferative responses and generation of CTL were significantly reduced by anti-CD80 + 86 treatment. Furthermore, anti-CD80 + 86 mAb preferentially inhibited the production of **interferon** (IFN)-gamma, but not IL-4 and IL-10, when cultures were assayed at 21 days. Although the anti-IL-12 mAb treatment alone inhibited the generation of cytotoxic T lymphocytes and IFN-gamma production in vitro, administration of anti-IL-12 mAb in vivo reversed the beneficial effects of anti-CD80 + 86 treatment on host survival post-BMT. The adverse effect of anti-IL-12 treatment seems to result from impairment of natural immunity and hematopoiesis, rather than as a consequence of an incomplete blockade of

T

helper (Th)1 responses. Our results suggest that the prevention of GVHD-induced death results from the efficient blockade of Th1 cell activation by the anti-CD80 + 86 treatment. However, further treatment is required for a complete prevention of GVHD, which seems to be partly mediated by Th2 cells.

L27 ANSWER 49 OF 63 MEDLINE

AN 96294793 MEDLINE

DN 96294793

TI Tumor necrosis factor alpha and interleukin-12 contribute to resistance to

the intracellular bacterium *Brucella abortus* by different mechanisms.

AU Zhan Y; Liu Z; Cheers C

CS Department of Microbiology, University of Melbourne, Parkville, Victoria, Australia.

SO INFECTION AND IMMUNITY, (1996 Jul) 64 (7) 2782-6.

Journal code: GO7. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199611

AB Both interleukin-12 (IL-12) and tumor necrosis factor alpha (TNF-alpha) are produced early in intracellular bacterial infection.

Depletion of either IL-12 or TNF-alpha by a single injection of specific antibody 4 h before the injection of *Brucella abortus* 19 led to the exacerbation of infection 2 weeks later. Whereas the effect of IL-12 depletion on resistance was persistent and exacerbation was still significant 6 weeks later, the bacterial numbers in mice depleted of TNF-alpha were similar to the bacterial numbers in control infected mice by 6 weeks postinfection. Massive splenomegaly, which is often seen in 2-week *Brucella*-infected mice, was not observed in IL-12- or TNF-alpha-depleted mice. Both IL-12- and TNF-alpha-depleted mice showed reduced cell accumulation in the spleen compared with the massive cell accumulation in control infected mice. Granuloma formation in livers was much reduced in IL-12-depleted mice but not in TNF-alpha-depleted mice. Gamma interferon (IFN-gamma) production by cells from TNF-alpha-depleted mice was not significantly different

from

that of cells from control infected mice. In contrast, the production of IFN-gamma by both CD4+ and CD8+ T cells from IL-12-depleted mice was greatly reduced, compared with that from control infected mice. This effect was still observed when the antibody injection was delayed for up to 7 days postinfection, but injections of anti-IL-12 antibody into mice with established *Brucella* infection had no significant effect on IFN-gamma production by T cells. Taken together, these results suggested that IL-12 contributed to resistance mainly via an IFN-gamma-dependent pathway and had a profound effect on the induction of acquired cellular resistance. In contrast, TNF-alpha was involved in resistance possibly via direct action on effector cells and may not be essential for the induction of acquired cellular resistance.

L27 ANSWER 50 OF 63 MEDLINE

AN 96294740 MEDLINE

DN 96294740

TI Interleukin-12-mediated resistance to *Trypanosoma cruzi* is dependent on tumor necrosis factor alpha and gamma interferon.

AU Hunter C A; Slifer T; Araujo F

CS Department of Immunology and Infectious Disease, Research Institute, Palo Alto Medical Foundation, California 94301, USA.

NC AI04717 (NIAID)

AI30320 (NIAID)

SO INFECTION AND IMMUNITY, (1996 Jul) 64(7) 2381-6.
 Journal code: GO7. ISSN: 0019-9567.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199611
 AB The aim of this study was to determine if interleukin-12 (IL-12) has a role in the immune response to Trypanosoma cruzi. Infection of BALB/c mice with the virulent Tulahuen strain of T. cruzi is characterized by a high-level parasitemia, pathology in the heart associated with the presence of amastigotes, and death during the acute phase of the disease. Administration of IL-12 to BALB/c mice infected with T. cruzi resulted in a reduced parasitemia and a significant delay in the time to death compared with those for infected controls. This protective effect was correlated with increased levels of gamma interferon (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) in serum. To determine if these cytokines were involved in the protective effects of IL-12, we treated infected mice with IL-12 alone or in combination with monoclonal antibodies specific for IFN-gamma or TNF-alpha. These antibodies antagonized the protective effect of exogenous IL-12. Treatment of infected mice with a polyclonal antibody specific for IL-12 resulted in a significant increase in parasitemia but did not affect the time to death. These latter studies demonstrate a role for endogenous IL-12 in resistance to T. cruzi. Together, our data identify an IL-12-mediated mechanism of resistance to T. cruzi, which is dependent on IFN-gamma and TNF-alpha.

L27 ANSWER 51 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 10
 AN 96171520 EMBASE
 DN 1996171520
 TI Lipoteichoic acid preparations of gram-positive bacteria induce interleukin-12 through a CD14-dependent pathway.
 AU Cleveland M.G.; Gorham J.D.; Murphy T.L.; Tuomanen E.; Murphy K.M.
 CS Washington Univ. School of Medicine, Box 8118, 660 S. Euclid, St. Louis, MO 63110, United States
 SO Infection and Immunity, (1996) 64/6 (1906-1912).
 ISSN: 0019-9567 CODEN: INFIBR
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 LA English
 SL English
 AB Interleukin 12 (IL-12) strongly augments gamma interferon production by natural killer (NK) and T cells. IL-12 also promotes effective cell-mediated immune responses, which are particularly important against intracellular bacteria such as Listeria monocytogenes. While the lipopolysaccharide (LPS) of gram-negative bacteria induces monocyte production of IL-12, the relevant gram-positive components which induce IL-12 production are uncharacterized. We used the human monocytic cell line THP-1 to study IL-12 induction by gram-positive bacteria. Muramyl dipeptides as well as the major muramyl tetrapeptide component of Streptococcus pneumoniae were inactive for inducing IL-12. In contrast, lipoteichoic acid (LTA), a predominant surface glycolipid of gram-positive bacteria, potently induced IL-12 p40 gene expression. A competitive LPS antagonist, Rhodobacter sphaeroides LPS, inhibited LTA-induced IL-12 production, suggesting a common pathway for LPS

and LTA in IL-12 activation. Pretreatment of cells with anti-CD14 monoclonal antibody blocked both LPS and LTA induction of IL-12 p40 expression. LTA also induced Th1 development in naive CD4 T cells by an IL-12-dependent mechanism, indicating direct induction of physiologic levels

of

IL-12. Together, these results show that LTA is a potent surface structure of gram-positive bacteria which induces IL-12 in monocytes through a CD14-mediated pathway.

L27 ANSWER 52 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
AN 96165859 EMBASE
DN 1996165859

TI IL-12 inhibits endotoxin-induced inflammation in the eye.

AU Whitcup S.M.; Rizzo L.V.; Lai J.C.; Hayashi S.; Gazzinelli R.; Chan C.-C.
CS National Eye Institute, 10 Center Drive, Bethesda, MD 20892-1858, United States

SO European Journal of Immunology, (1996) 26/5 (995-999).
ISSN: 0014-2980 CODEN: EJIMAF

CY Germany

DT Journal; Article

FS 012 Ophthalmology

026 Immunology, Serology and Transplantation

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Interleukin-12 (IL-12) is a heterodimeric cytokine that induces interferon (IFN)- γ , production and an increased generation of Th1 cells. Both IL-12 and IL-12 antagonists are being studied for the treatment of allergic reactions, autoimmune disease and malignancy. The goal of the present experiments was to examine the importance of IL-12 in endotoxin-induced ocular inflammation. The number of inflammatory cells infiltrating eyes with endotoxin-induced uveitis (EIU) was significantly increased in animals treated with intraperitoneal anti-IL-12 antibody when compared to control animals, but there was no difference in infiltrating inflammatory cells in the eyes of animals treated with IL-12 when compared to controls. In contrast, intraocular injection of IL-12 significantly inhibited the development of endotoxin-induced intraocular inflammation. The infiltrating inflammatory cells were reduced in the eyes of animals receiving intraocular IL-12 when compared to controls. Cytokine analysis of the aqueous humor obtained from eyes with EIU showed increased levels of IFN- γ and decreased levels of IL-6 in eyes receiving intraocular IL-12. These data show that IL-12 has an inhibitory effect on endotoxin-induced inflammation in the eye and suggest that IL-12 can have an immunoregulatory function in some forms of inflammatory disease.

L27 ANSWER 53 OF 63 MEDLINE

AN 96196113 MEDLINE

DN 96196113

TI Interleukin-12 decreases human immunodeficiency virus type 1 replication in human macrophage cultures reconstituted with autologous peripheral blood mononuclear cells.

AU Akridge R E; Reed S G

CS Infectious Disease Research Institute, Seattle, Washington, 98104, USA.

NC AI-27711 (NIAID)

TW-00070 (FIC)

SO JOURNAL OF INFECTIOUS DISEASES, (1996 Mar) 173 (3) 559-64.
Journal code: IH3. ISSN: 0022-1899.

sufficient to trigger arthritis. Attempts to show a role for endogenous IL-12 in DBA/1 mice immunized with collagen with mycobacteria as adjuvant gave no reliable results. Whereas anti-IL-12 treatment delayed the onset and ameliorated the disease in some experiments, it failed to do so in other experiments, or, control reagents also had some effect. A slight inhibition of collagen-specific IgG2a synthesis was observed in most experiments in the sera of anti-IL-12-treated mice. Taken together, the results show that exogenous IL-12 can promote arthritis via its direct effect on T cells and its effect on **antibody** production, which is at least in part IFN-gamma-dependent. On the other hand, whether or not endogenous IL-12 is involved in the adjuvant effect of mycobacteria needs further clarification.

L27 ANSWER 55 OF 63 MEDLINE

AN 96042126 MEDLINE

DN 96042126

TI **Antibodies** to interleukin 12 abrogate established experimental colitis in mice.

AU Neurath M F; Fuss I; Kelsall B L; Stuber E; Strober W

CS Mucosal Immunity Section, National Institutes of Health/National Institute

of Allergy and Infectious Diseases/LCI, Bethesda, Maryland 20892-1890, USA..

SO JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Nov 1) 182 (5) 1281-90.

Journal code: I2V. ISSN: 0022-1007.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199602

AB In this study, we describe a novel murine model of chronic intestinal inflammation induced by the hapten reagent 2,4,6-trinitrobenzene sulfonic acid (TNBS). Rectal application of low doses of TNBS in BALB/c and SJL/J mice resulted in a chronic transmural colitis with severe diarrhea,

weight

loss, and rectal prolapse, an illness that mimics some characteristics of Crohn's disease in humans. The colon of TNBS-treated mice on day 7 was marked by infiltration of CD4+ T cells; furthermore, in situ polymerase chain reaction studies revealed high levels of **interferon** (IFN)-gamma mRNA in diseased colons. Isolated lamina propria (LP) CD4+ T cells from TNBS-treated mice stimulated with anti-CD3 and anti-CD28 **antibodies** exhibited a Th1 pattern of cytokine secretion: a 20-50-fold increase in IL-2 and IFN-gamma levels and a 5-fold decrease in IL-4 levels as compared with those of stimulated LP CD4+ T cells from control BALB/c mice. Administration of monoclonal anti-IL-12 **antibodies** to the TNBS-treated mice both early (at 5 d) and late (at 20 d) after induction of colitis led to a striking improvement in both the clinical and histopathological aspects of the disease and frequently abrogated the established colitis completely. Furthermore, LP CD4+ T cells isolated from anti-IL-12 -treated mice failed to secrete IFN-gamma upon in vitro stimulation. In summary, the data demonstrate the pivotal role of IL-12 and IFN-gamma in a TNBS-induced murine model of chronic intestinal inflammation. Furthermore, they suggest the potential utility of anti-IL-12 **antibodies** in patients with Crohn's disease.

L27 ANSWER 56 OF 63 MEDLINE

AN 95255423 MEDLINE

DN 95255423

TI Transforming growth factor-beta inhibits interleukin-12-induced production

of **interferon**-gamma by natural killer cells: a role for transforming growth factor-beta in the regulation of T cell-independent

resistance to Toxoplasma gondii.
AU Hunter C A; Bermudez L; Beernink H; waegell w; Remington J S
CS Department of Immunology and Infectious Diseases, Palo Alto Medical
Foundation, California, USA..
NC A104717
A130230
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Apr) 25 (4) 994-1000.
Journal code: EN5. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199508
AB Severe-combined immune deficient (SCID) mice have been found to resist
infection with the intracellular protozoan parasite Toxoplasma gondii via
interleukin (IL)-12 stimulation of **interferon**
(IFN)-gamma production by natural killer (NK) cells. Previously, we
demonstrated the presence of increased levels of transcripts for
transforming growth factor-beta (TGF-beta) in the brains and lungs of
SCID
mice infected with T. gondii, leading us to investigate the role of
TGF-beta in the mechanism of resistance to T. gondii in these mice.
Stimulation of splenocytes from SCID mice with heat-killed T. gondii
resulted in production of low levels of IFN-gamma and a two to threefold
increase in levels of TGF-beta in the culture supernatants. Production of
IFN-gamma in these cultures was increased three to fourfold by addition
of
anti-TGF-beta **antibody**. Stimulation of splenocytes from SCID
mice with IL-12 in combination with either TNF-alpha
or IL-1 beta resulted in production of high levels of IFN-gamma. Addition
of TGF-beta to these cultures inhibited production of IFN-gamma in a
dose-dependent manner. Immunohistochemical studies revealed increased
levels of TGF-beta protein in the spleens of SCID mice 5 days after oral
infection with the ME49 strain of T gondii, and brains of SCID mice at 18
days post-infection. However, no difference was detected in the levels of
TGF-beta transcripts in the spleens of uninfected mice or mice infected
for 5 days. To test whether TGF-beta could antagonize IL-
12 mediated resistance to T. gondii in vivo, we administered
TGF-beta to SCID mice infected with T. gondii. This treatment resulted in
earlier mortality of infected mice and significantly reduced the ability
of exogenous IL-12 to delay time-to-death.
Administration of anti-TGF-beta to SCID mice, beginning 24 h prior to
infection and every 2 days thereafter, delayed significantly
time-to-death. Together, our data demonstrate that TGF-beta antagonizes
the ability of IL-12 to stimulate production of
IFN-gamma by splenocytes from SCID mice, and suggest a role for TGF-beta
in regulation of T cell-independent resistance to T. gondii.

L27 ANSWER 57 OF 63 MEDLINE
AN 95105717 MEDLINE
DN 95105717
TI Prevention of experimental autoimmune encephalomyelitis by
antibodies against interleukin 12.
AU Leonard J P; Waldburger K E; Goldman S J
CS Genetics Institute, Cambridge, Massachusetts 02140.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Jan 1) 181 (1) 381-6.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199504
AB Experimental allergic encephalomyelitis (EAE) is an autoimmune disease of
the central nervous system that can be transferred to naive mice via CD4+
T cells isolated from appropriately immunized mice. We have evaluated the

have

effects of recombinant murine interleukin 12 (rmIL-12), a potent inducer of interferon gamma (IFN-gamma) and promoter of Th1 cell development, on the course of adoptively transferred EAE. The transfer of lymph node cells (LNC) isolated from proteolipid protein (PLP)-primed animals and stimulated in vitro with PLP to naive mice resulted in a progressive paralytic disease culminating in complete hind limb paralysis in the majority of the recipients. When mice were injected with LNC that had been stimulated in vitro with PLP in the presence of rmIL-12, the subsequent course of disease was more severe and prolonged. The addition of rmIL-12 during the in vitro stimulation with PLP resulted in a 10-fold increase in IFN-gamma and a 2-fold increase in tumor necrosis factor

(TNF)

alpha in the supernatants, relative to LNC stimulated with PLP alone. However, neutralization of IFN-gamma or TNF-alpha in vitro with specific antibodies did not abrogate the ability of rmIL-12 to exacerbate the subsequent disease. Similarly, mice treated with rmIL-12 in vivo

after

the transfer of antigen-stimulated LNC developed a more severe and prolonged course of disease compared with vehicle-treated control

animals.

In contrast, treatment of mice with an antibody to murine IL-12 after cell transfer completely prevented paralysis, with only 40% of the mice developing mild disease. These results demonstrate that in vitro stimulation of antigen primed LNC with PLP and rmIL-12 enhances their subsequent encephalitogenicity. Furthermore, inhibition of endogenous IL-12 in vivo after LNC transfer prevented paralysis, suggesting that endogenous IL-12 plays a pivotal role in the pathogenesis of this model of autoimmune disease.

L27 ANSWER 58 OF 63 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1995:345685 BIOSIS

DN PREV199598359985

TI Strategies for the development of a vaccine against ringworm.

AU Smith, J. M. B. (1); Griffin, J. F. T.

CS (1) Dep. Microbiol., Univ. Otago, Dunedin New Zealand

SO Journal of Medical & Veterinary Mycology, (1995) Vol. 33, No. 2, pp. 98-91.

ISSN: 0268-1218.

DT Article

LA English

AB Resolution of lesions and subsequent protection against ringworm is primarily associated with the development of a cell-mediated immune (CMI) response, in which stimulation of Type-1 lymphocytes and cytokines such

as

interleukin-2 (IL-2), IL-12 and interferon gamma are significant. Type-2 lymphocyte activation and antibody formation seem a feature of chronic disease states, rather than protection, and are antagonistic to a Type-1 cell response. Initial studies on ringworm vaccines should be directed at identifying

and

characterizing dermatophyte antigens elaborated during spore germination and early hyphal growth, and the method of their presentation which best potentiates Type-1 cell-associated events, and primes the recipient for a subsequent CMI response.

L27 ANSWER 59 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 12

AN 95187189 EMBASE

DN 1995187189

TI Strategies for the development of a vaccine against ringworm.

AU Smith J.M.B.; Griffin J.F.T.

CS Department of Microbiology, University of Otago, Dunedin, New Zealand

SO Journal of Medical and Veterinary Mycology, (1995) 33/2 (87-91).

ISSN: 0268-1218 CODEN: JMVMEQ

CY United Kingdom

DT Journal; General Review
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 037 Drug Literature Index
 LA English
 SL English
 AB Resolution of lesions and subsequent protection against ringworm is primarily associated with the development of a cell-mediated immune (CMI) response, in which stimulation of Type-1 lymphocytes and cytokines such as interleukin-2 (IL-2), **IL-12** and **interferon** gamma are significant. Type-2 lymphocyte activation and **antibody** formation seem a feature of chronic disease states, rather than protection, and are **antagonistic** to a Type-1 cell response. Initial studies on ringworm vaccines should be directed at identifying and characterizing dermatophyte antigens elaborated during spore germination and early hyphal growth, and the method of their presentation which best potentiates Type-1 cell-associated events, and primes the recipient for a subsequent CMI response.

L27 ANSWER 60 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 13
 AN 95103116 EMBASE
 DN 1995103116
 TI Rationale for cytokine and anti-cytokine therapy of Candida albicans infection.
 AU Mencacci A.; Cenci E.; Spaccapelo R.; Tonnetti L.; Romani L.; Puccetti P.; Bistoni F.
 CS Dept. of Exp. Med./Biochem. Sciences, Microbiology Section, University of Perugia, Via del Giochetto, 06122 Perugia, Italy
 SO Journal de Mycologie Medicale, (1995) 5/1 (25-30).
 ISSN: 1156-5233 CODEN: JMYME5
 CY France
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 037 Drug Literature Index
 LA English
 SL English; French
 AB Introduction: Systemic infection with Candida albicans results in different patterns of disease depending on host genetic and yeast strain factors, with a correlation between disease outcome and the predominant T helper (Th) cell response. In particular, healing infection is associated with strong delayed type hypersensitivity (DTH), high levels of interleukin-2 (IL-2) and **interferon** gamma (IFN-.gamma.) and low levels of IL-4 and IL-10, thus indicating the predominant involvement of the Th1 subset. In non healing infection, a reverse pattern is observed in which susceptibility to C. albicans is accompanied by the detection of CD4+ Th2 cells producing IL-4, IL-5 and IL-10 and mediating humoral and allergic responses. The various experimental C. albicans infection models, described in the literature, are discussed and new personal experimental data are presented. Methods: To gain insight into the ability of cytokines to influence the development of protective or exacerbative CD4+ Th cells in systemic candidiasis, we administered anti-cytokine monoclonal **antibodies** (mAb) or cytokine **antagonists** or cytokines such as, **IL-12**, IL-4 IL-10 and IFN-.gamma. in vivo in experimental models of healing and non healing infections. These models were obtained by inoculating low virulence C. albicans (PCA-2) into CD2F1 mice (healing infection) or susceptible DBA/2 mice (non healing infection) or highly virulent C. albicans (CA-6) into CD2F1 mice (non healing

infection). Results: A conversion from a non healing to a healing phenotype was obtained by administering IL-4 neutralizing mAb or soluble IL-4 receptor to CD2F1 mice challenged with CA-6, or by administering anti-IL-10 mAb to PCA-2 infected DBA/2 mice. Conversely, the administration of anti-IFN-.gamma. and anti-IL-12 to healer mice, while not affecting the outcome of primary infection, impaired the development of acquired resistance to a subsequent lethal challenge which was accompanied by the detection of Th2-mediated responses. Conclusion: The current understanding of cytokine-dependent, cross-regulatory Th1/Th2 responses in murine candidiasis may pave the way for possible therapeutic strategies aimed at restoring protective cell-mediated immunity in human infection. In fact, some cytokines (IL-12 and IL-4), more than others (IFN-.gamma. and IL-10), exert potent and opposing regulatory effects on the induction of

a

protective cell-mediated anticandidal response. Therefore, cytokine replacement therapy or, conversely, cytokine neutralization could modify resistance to infection. However, because of the complexity of their actions, the use of recombinant cytokines may lead to pleiotropic, redundant, or undesirable side effects. Perhaps more fruitful will be an approach based on the use of specific cytokine **antagonists**.

L27 ANSWER 61 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 94092558 EMBASE

DN 1994092558

TI Biological response modifiers and parasitic infections: Experimental aspects of toxoplasmosis.

AU Beaman M.H.

CS University Department of Medicine, Fremantle Hospital, P.O. Box 480, Fremantle, WA 6160, Australia

SO Canadian Journal of Infectious Diseases, (1994) 5/SUPPL. A (47A-50A). ISSN: 1180-2332 CODEN: CJDIES

CY Canada

DT Journal; Conference Article

FS 004 Microbiology

030 Pharmacology

037 Drug Literature Index

LA English

SL English; French

AB Parasitic infections are important causes of disease in the developing world and, since the advent of AIDS, the developed world. Over the past decade, in vitro and in vivo studies have established the important role that biological response modifiers play in pathogenesis of parasitic disease. These basic studies have resulted in successful clinical trials of **interferon** gamma (IFN-.gamma.) in human leishmaniasis. Toxoplasmic encephalitis is a major opportunistic infection in patients with AIDS, and current therapy is often problematic. IFN-.gamma. has been shown in in vitro and in vivo animal studies to be critical for host defence against *Toxoplasma gondii*. Tumour necrosis factor alpha plays a critical role in mediating IFN-.gamma. effect in vitro, but its role in vivo is under further study. Interleukin (IL)-6 and IL-10 have both recently been shown to enhance *T gondii* replication in vitro and to antagonize the beneficial effects of IFN-.gamma.. In addition, in certain mouse strains, IL-6 has been shown to worsen mortality from *T gondii* infection. Future strategies for therapy of *T gondii* may include administration of exogenous IFN-.gamma. or IL-12 with or without **antibody** to **antagonistic** cytokines such as IL-6 (or possibly IL-10).

L27 ANSWER 62 OF 63 MEDLINE

AN 94052129 MEDLINE

DN 94052129

TI Interleukin 12 acts directly on CD4+ T cells to enhance priming for **interferon** gamma production and diminishes interleukin 4 inhibition of such priming.

AV Seder R A; Gazzinelli R; Sher A; Paul W E
 CS Laboratory of Immunology, National Institute of Allergy and Infectious
 Diseases, National Institutes of Health, Bethesda, MD 20892.
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
 AMERICA, (1993 Nov 1) 90 (21) 10188-92.
 Journal code: PV3. ISSN: 0027-8424.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199402

AB Naive CD4+ T cells produce interleukin 2 (IL-2) but little IL-4 or
 interferon gamma (IFN-gamma). In vitro, they develop into IL-4 or
 IFN-gamma producers depending on the conditions of the priming culture.
 Using T-cell receptor transgenic CD4+ T cells, the role of IL-
 12 and IL-4 in antigen-specific priming was examined. IL
 -12 substantially enhanced the ability of naive CD4+ T cells to
 develop into cells that produced IFN-gamma upon restimulation. However,

it

was not essential since anti-IL-12 antibodies
 failed to block the priming for IFN-gamma observed in the absence of
 exogenous IL-12. When both IL-12
 and IL-4 were present in the priming culture, IL-12
 did not inhibit priming for IL-4 production. In contrast, IL-4 diminished
 but did not abolish priming for IFN-gamma production. In an accessory
 cell-independent priming system, IL-12 strikingly
 augmented priming for IFN-gamma production, indicating that it acts
 directly on T cells. IFN-gamma itself did not enhance priming for
 IFN-gamma production in either accessory cell-dependent or independent
 systems. In an accessory cell-dependent system, the IL-
 12-mediated enhancement was not blocked by adding neutralizing
 anti-IFN-gamma monoclonal antibody. However, in an accessory
 cell-independent system, anti-IFN-gamma antibody did inhibit
 priming for IFN-gamma production leaving open a role for IFN-gamma in the
 priming process. These data indicate that IL-12 has a
 major effect on the inductive phase of T-cell priming by enhancing
 commitment to IFN-gamma production and thus can profoundly influence the
 state of immunity that develops.

L27 ANSWER 63 OF 63 MEDLINE

AN 93380489 MEDLINE

DN 93380489

TI The interleukin-12 subunit p40 specifically inhibits effects of the
 interleukin-12 heterodimer.

AU Mattner F; Fischer S; Guckes S; Jin S; Kaulen H; Schmitt E; Rude E;
 Germann T

CS Institut fur Immunologie, Mainz, Germany..

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1993 Sep) 23 (9) 2202-8.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199312

AB The recently discovered cytokine interleukin (IL)-12
 is a heterodimeric protein of two disulfide-bonded subunits of 35 and 40
 kDa. IL-12 has multiple effects on T cells and natural
 killer (NK) cells. In particular it appears to be a major factor for the
 development of cellular immunity. So far activity of the single subunits
 alone has not been described, however their expression is regulated
 independently. In this report we demonstrate for the first time that the
 mouse IL-12 subunit p40 (IL-12p40) specifically
 antagonizes the effects of the IL-12 heterodimer in
 different assay systems. The proliferation of mouse splenocytes activated
 by phorbol ester and IL-12 was inhibited by IL-12p40,

whereas the proliferation induced by phorbol ester and IL-2 was not affected. Furthermore, the synthesis of interferon (IFN) gamma by mouse splenocytes activated with IL-2 and IL-12 was suppressed by IL-12p40. Purified mouse splenic CD4+ T cells produced IFN-gamma upon activation with plate-bound anti-CD3 monoclonal antibody which was enhanced more than tenfold in the presence of IL-12. In this system IL-12p40 inhibited only the enhancement caused by IL-12 but not IFN-gamma synthesis of CD4+ T cells stimulated with anti-CD3 alone. Moreover, IL-12p40 inhibited the effects of IL-12 on differentiated T helper type 1 (Th1) cells. IFN-gamma production by Th1 cells induced in a T cell receptor-independent way by macrophages and

IL-2

or macrophages and IL-12 was greatly reduced by IL-12p40 providing evidence for the endogenous synthesis of IL-12 in the Th1 cell, macrophage and IL-2 co-cultures. The specificity of inhibition was clearly demonstrated in the homotypic aggregation assay of Th1 cells. Incubation of Th1 cells with either IL-2 and IL-12 or IL-2 and tumor necrosis factor induces LFA-1/ICAM-1-dependent aggregation. Only IL-2 + IL-12 but not IL-2 + tumor necrosis factor-induced aggregation was inhibited in a dose-dependent manner by IL-12p40. Thus, the IL-12 subunit p40 appears to be a specific inhibitor for the IL-12 heterodimer.

=> d bib ab 1-39

L27 ANSWER 1 OF 63 USPATFULL

AN 2001:33443 USPATFULL

TI Translation initiation factor 4AIII and methods of use thereof

IN Hemmati-Brivanlou, Ali, New York, NY, United States

Weinstein, Daniel C., New York, NY, United States

PA The Rockefeller University, New York, NY, United States (U.S. corporation)

PI US 6197947 20010306

AI US 1999-318443 19990525 (9)

PRAI US 1998-87575 19980601 (60)

DT Utility

EXNAM Primary Examiner: Wortman, Donna C.; Assistant Examiner: Zeman, Robert

LREP Darby & Darby

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 2274

AB The present invention provides a vertebrate translation initiation factor (eIF-4AIII), that plays a role in the differentiation of an embryonic cell to an epidermal cell. This translation initiation factor interacts with BMP-4 in a positive regulatory loop. The nucleic acid

and

amino acid sequences are also disclosed. Also disclosed are methods of using the translation initiation factor, nucleic acids encoding the same, and corresponding antibodies and the like.

L27 ANSWER 2 OF 63 USPATFULL

AN 2001:14618 USPATFULL

TI Cyclin D binding factor, and uses thereof

IN Sherr, Charles J., Memphis, TN, United States

Hirai, Hiroshi, Memphis, TN, United States

Inoue, Kazushi, Memphis, TN, United States

Bodner, Sara M., Memphis, TN, United States

PA St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)

PI US 6180763 20010130

AI US 1997-928941 19970912 (8)
RLI Continuation-in-part of Ser. No. US 1997-857011, filed on 15 May 1997,
now abandoned
PRAI US 1996-17815 19960516 (60)
DT Utility
EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Longton,
Enrique
LREP Klauber & Jackson
CLMN Number of Claims: 39
ECL Exemplary Claim: 1
DRWN 26 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 3451

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention discloses a direct interaction between D-type cyclins and
a novel myb-like transcription factor, DMP1, which specifically
interacts with cyclin D2. The present invention also provides evidence
that D-type cyclins regulate gene expression in an RB-independent
manner. Also included is DMP1, the transcription factor composed of a
central DNA-binding domain containing three atypical myb repeats
flanked

by highly acidic segments located at its amino- and carboxyterminal
ends. The invention includes amino acid sequences coding for DMP1, and
DNA and RNA nucleotide sequences that encode the amino acid sequences.

A use of DMP1 as a transcription factor is disclosed due to its
specificity in binding to oligonucleotides containing the nonamer
consensus sequence CCCG(G/T)ATGT. In this aspect of the invention, DMP1
when transfected into mammalian cells, activates the transcription of a
reporter gene driven by a minimal promoter containing concatamerized
DMP1 binding sites.

L27 ANSWER 3 OF 63 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1

AN 2000:484772 BIOSIS

DN PREV200000484772

TI Methods and compositions for modulating responsiveness to
corticosteroids.

AU Sekut, Les (1); Carter, Adam; Ghayur, Tariq; Banerjee, Subhashis; Tracey,
Daniel E.

CS (1) Westborough, MA USA

ASSIGNEE: BASF Aktiengesellschaft, Rheinland Pfalz, Germany

PI US 6054487 April 25, 2000

SO Official Gazette of the United States Patent and Trademark Office
Patents,

(Apr. 25, 2000) Vol. 1233, No. 4, pp. No pagination. e-file.

ISSN: 0098-1133.

DT Patent

LA English

AB Method for modulating responsiveness to corticosteroids in a subject are
provided. In the method of the invention, an agent which antagonizes a
factor that regulates production of IFN-gamma in the subject is
administered to the subject in combination with a corticosteroid such

that
responsiveness of the subject to the corticosteroid is modulated as
compared to when a corticosteroid alone is administered to the subject.

In
one embodiment, the agent is an **interferon-gamma** inducing factor
(IGIF) **antagonist**. In another embodiment, the agent is an
interleukin-12 (IL-12) **antagonist**. In a
preferred embodiment, the agent is an inhibitor of a caspase family
protease, preferably an ICE inhibitor. In another preferred embodiment,
the agent is an anti-IL-12 monoclonal **antibody**
. Other preferred agents include phosphodiesterase IV inhibitors and
beta-2 agonists. The methods of the invention can be used in the
treatment

of a variety of inflammatory and immunological diseases and disorders.

Pharmaceutical compositions comprising an agent which antagonizes a factor

that regulates production of IFN-gamma in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred composition comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L27 ANSWER 4 OF 63 USPATFULL

AN 2000:138395 USPATFULL

TI Treatment of T-helper cell type 2-mediated immune disease by retinoid antagonists

IN Bollag, Werner, Basel, Switzerland
Klaus, Michael, Weil am Rhein, Germany, Federal Republic of
Panina-Bordignon, Paola, Milan, Italy
Sinigaglia, Francesco, Milan, Italy

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 6133309 20001017

AI US 1998-189189 19981110 (9)

PRAI EP 1997-119776 19971112

DT Utility

EXNAM Primary Examiner: Travers, Russell

LREP Johnston, George W.; Epstein, William H.; Parise, John P.

CLMN Number of Claims: 37

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 780

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Retinoids with retinoid receptor **antagonistic** activity, pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, have been found efficacious in treating T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases.

L27 ANSWER 5 OF 63 USPATFULL

AN 2000:134732 USPATFULL

TI Nitrobenzylmercaptapurineriboside (NBMPR)-insensitive, equilibrative, nucleoside transport protein, nucleic acids encoding the same and methods of use

IN Belt, Judith A., Memphis, TN, United States

Crawford, Charles R., Memphis, TN, United States

PA St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)

PI US 6130065 20001010

AI US 1998-58389 19980409 (9)

PRAI US 1997-43659 19970411 (60)

DT Utility

EXNAM Primary Examiner: Carlson, Karen Cochrane; Assistant Examiner: Srivastava, Devesh

LREP Klauber & Jackson

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 11 Drawing Page(s)

LN.CNT 3642

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An isolated NBMPR-insensitive equilibrative nucleoside transport protein

(iENTP) and the nucleic acid encoding it is disclosed. The iENTP can be used in screening assays to identify both natural nucleoside permeants and/or inhibitors and analogs thereof. In addition, transfected or transduced cell lines are disclosed which use the iENTP as the sole nucleoside transport protein. Methods of employing such cell lines for drug screening are also included. Furthermore methods of using hematopoietic stem cells transduced with an iENTP in a chemotherapy protocol is also described. In addition, methods of using these cells

to

selectively express a heterologous gene for gene therapy is disclosed.

L27 ANSWER 6 OF 63 USPATFULL
AN 2000:74387 USPATFULL
TI Cyclin-C variants, and diagnostic and therapeutic uses thereof
IN Lahti, Jill M., Cordova, TN, United States
Kidd, Vincent J., Cordova, TN, United States
PA St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)
PI US 6075123 20000613
AI US 1997-867381 19970602 (8)
PRAI US 1996-18614 19960603 (60)
DT Utility
EXNAM Primary Examiner: Park, Hankyel
LREP Klauber & Jackson
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 3718

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention includes alternatively and partially spliced cyclin C mRNAs, recombinant DNA and the truncated protein (a truncated cyclin C) they encode. The alternatively spliced mRNAs result from an insertion of unique exons containing premature termination codons. The partially spliced mRNAs result from an insertion of additional coding sequence derived from exons. One aspect of the present invention is the demonstration that at least one of the alternatively spliced cyclin C mRNAs is produced in a cell cycle dependent fashion, as is the novel truncated cyclin box protein that it encodes. Truncated cyclin C acts

as
an endogenously encoded cyclin C inhibitor by negatively regulating cyclin C/cdk8 complex activity, in much the same way as the cyclin dependent protein kinase inhibitors that inhibit the D-type cyclins, cyclin A and cyclin E.

L27 ANSWER 7 OF 63 USPATFULL
AN 2000:64711 USPATFULL
TI Growth factor inducible serine/threonine phosphatase fin13
IN Guthridge, Mark A., South Australia, Australia
Basilico, Claudio, New York, NY, United States
Bellosta, Paola, New York, NY, United States
PA New York University, New York, NY, United States (U.S. corporation)
PI US 6066485 20000523
AI US 1997-935855 19970923 (8)
RLI Continuation-in-part of Ser. No. US 1997-822701, filed on 21 Mar 1997, now patented, Pat. No. US 5976853
PRAI US 1996-13792 19960321 (60)
DT Utility
EXNAM Primary Examiner: Nashed, Nashaat
LREP Klauber & Jackson
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 23 Drawing Page(s)
LN.CNT 4106

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel serine/threonine phosphatase, FIN13, which includes a collagen-homology domain, an acidic box domain, a catalytic domain, and a putative nuclear translocation sequence. The present invention

further
relates to the modulation of cellular proliferation, by regulating the activity of the novel serine/threonine phosphatase. Thus, the invention provides the phosphatase, nucleic acids encoding the phosphatase, oligonucleotides specific for such nucleic acids, **antibodies** to the phosphatase, and methods for increasing (or decreasing) the activity of the phosphatase to inhibit (or enhance) cellular

proliferation and, thus, tissue growth. Various diagnostic and therapeutic aspects of the invention particularly relate to detection and treatment of hyperproliferative disorders, neoplasms, and tumors.

In specific examples, FIN13 is expressed in proliferating cells, notably germ cells of the testes. Increased levels of expression of FIN13 in transfected cells results in a decrease in the cell growth rate.

L27 ANSWER 8 OF 63 USPATFULL

AN 2000:53913 USPATFULL

TI Clock gene and methods of use thereof

IN Young, Michael W., Old Tappan, NJ, United States

Kloss, Brian, New York, NY, United States

Blau, Justin, New York, NY, United States

Price, Jeffrey, Morgantown, WV, United States

PA The Rockefeller University, New York, NY, United States (U.S. corporation)

PI US 6057129 20000502

AI US 1998-100664 19980619 (9)

DT Utility

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Klauber & Jackson

CLMN Number of Claims: 31

ECL Exemplary Claim: 1

DRWN 32 Drawing Figure(s); 17 Drawing Page(s)

LN.CNT 4329

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides isolated nucleic acids and/or recombinant

DNA molecules that encode the clock protein DOUBLETIME. The present invention further provides both isolated and/or recombinant DOUBLETIME.

In addition, the present invention provides antibodies to DOUBLETIME. Methods of using the nucleic acids, proteins and antibodies of the present invention, including as therapeutics are also provided.

L27 ANSWER 9 OF 63 USPATFULL

AN 2000:27752 USPATFULL

TI Promoter of the cdc25B gene, its preparation and use

IN Koerner, Kathrin, Marburg, Germany, Federal Republic of

Mueller, Rolf, Marburg, Germany, Federal Republic of

Sedlacek, Hans-Harald, Marburg, Germany, Federal Republic of

PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic

of (non-U.S. corporation)

PI US 6033856 20000307

AI US 1998-39555 19980316 (9)

PRAI DE 1997-19710643 19970314

DT Utility

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Foley & Lardner

CLMN Number of Claims: 43

ECL Exemplary Claim: 42

DRWN 10 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 2848

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides the promoter of the cdc25B gene, a process for finding cdc25B promoters and methods for using the promoters for preparing a pharmaceutical.

L27 ANSWER 10 OF 63 USPATFULL

AN 2000:15485 USPATFULL

TI Nucleic acid encoding an altered telomere repeat binding factor

IN de Lange, Titia, New York, NY, United States

van Steensel, Bas, New York, NY, United States

PA Bianchi, Alessandro, New York, NY, United States
The Rockefeller University, New York, NY, United States (U.S.
corporation)
PI US 6022709 20000208
AI US 1998-209605 19981211 (9)
RLI Division of Ser. No. US 1997-800264, filed on 13 Feb 1997, now
patented,
Pat. No. US 5859183
DT Utility
EXNAM Primary Examiner: McKelvey, Terry
LREP Klauber & Jackson
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 29 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 3788
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an isolated altered vertebrate telomere
repeat binding factor (A-TRF) that hinders the binding of a TRF to its
specific telomere repeat sequence. Also included are the corresponding
nucleic acids that encode the A-TRFs of the present invention, as well
as the heterodimers formed by the association of an A-TRF with a TRF.

In
addition, pharmaceutical compositions containing the A-TRFs for
treatment of diseases such as ataxia telangiectasia are also included.
Methods of making, purifying and using the A-TRFs of the present
invention are described. In addition, drug screening assays to identify
drugs that mimic and/or complement the effect of the A-TRFs are
presented.

L27 ANSWER 11 OF 63 USPATFULL

AN 2000:12629 USPATFULL
TI Nucleic acid encoding an altered telomere repeat binding factor 2
IN De Lange, Titia, New York, NY, United States
Van Steensel, Bas, Seattle, WA, United States
Bianchi, Alessandro, Geneve, Switzerland
PA The Rockefeller University, New York, NY, United States (U.S.
corporation)
PI US 6020166 20000201
AI US 1999-273378 19990322 (9)
RLI Division of Ser. No. US 1998-18628, filed on 4 Feb 1998, now patented,
Pat. No. US 5917019 which is a continuation-in-part of Ser. No. US
1997-800264, filed on 13 Feb 1997, now patented, Pat. No. US 5859183,
issued on 12 Jan 1999
DT Utility
EXNAM Primary Examiner: McKelvey, Terry
LREP Klauber & Jackson
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 69 Drawing Figure(s); 24 Drawing Page(s)
LN.CNT 5301
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an isolated altered vertebrate telomere
repeat binding factor (A-TRFs). Also included are the corresponding
nucleic acids that encode the A-TRFs of the present invention, as well
as the heterodimers formed by the association of an A-TRF with a TRF.

In
addition, pharmaceutical compositions containing the A-TRFs for
treatment of diseases such as ataxia telangiectasia are also included.
Methods of making, purifying and using the A-TRFs of the present
invention are described. In addition, drug screening assays to identify
drugs that mimic and/or complement the effect of the A-TRFs are
presented.

L27 ANSWER 12 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000089594 EMBASE

TT Host immune reactivity determines the efficacy of combination immunotherapy and antifungal chemotherapy in candidiasis.
 AU Mencacci A.; Cenci E.; Bacci A.; Bistoni F.; Romani L.
 CS Dr. L. Romani, Microbiology Section, Dept. of Exptl. Med./Biochem. Sci., University of Perugia, Via del Giochetto, 06122 Perugia, Italy. Iromani@unipg.it
 SO Journal of Infectious Diseases, (2000) 181/2 (686-694).
 Refs: 60
 ISSN: 0022-1899 CODEN: JIDIAQ
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 006 Internal Medicine
 037 Drug Literature Index
 LA English
 SL English
 AB In immunocompetent mice with candidiasis, successful therapy with amphotericin B and fluconazole relies on the induction of protective, T helper (Th) type 1 responses, an effect potentiated by concomitant interleukin (IL)-4 neutralization. To assess the therapeutic efficacy of combined treatments with antifungals and immunomodulators in conditions

of immunosuppression, leukopenic or neutropenic mice with disseminated candidiasis were treated with amphotericin B or fluconazole alone or in combination with soluble IL-4 receptor (sIL-4R) or recombinant (r) IL-12 or IL-10 neutralizing monoclonal antibodies. We found that (1) the synergistic effect of sIL-4R and antifungals is retained in immunocompromised mice; (2) synergism with amphotericin B was superior to that with fluconazole, particularly in leukopenic mice; (3) rIL-12 synergized with fluconazole in neutropenic mice; and (4) IL-10 neutralization was always of limited efficacy. This study indicates that the therapeutic efficacy of antifungals is differentially potentiated by cytokines or cytokine antagonists and is influenced by host immune reactivity.

L27 ANSWER 13 OF 63 MEDLINE

AN 2000087332 MEDLINE

DN 20087332

TI Role of interferon-gamma and nitric oxide in pulmonary edema and death induced by lipopolysaccharide.

AU Heremans H; Dillen C; Groenen M; Matthys P; Billiau A

CS Laboratory of Immunobiology, Rega Institute, University of Leuven, Faculty

of Medicine, Leuven, Belgium.. Hubertine.Heremans@rega.kuleuven.ac.be

SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2000 Jan)

161

(1) 110-7.

Journal code: BZS. ISSN: 1073-449X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200005

EW 20000501

AB Mice given lipopolysaccharide (LPS) intravenously developed lung edema, which was maximum after 6 h. Tumor necrosis factor, interleukin 12 (IL-12), IL-6, and interferon-gamma (IFN-gamma) appeared in the serum, and levels of nitrogen oxide (NO) derivatives were increased in serum and bronchoalveolar fluid. Mice pretreated with neutralizing anti-IFN-gamma antibodies had lower serum levels of IFN-gamma, and fewer died. However, levels of other cytokines and NO derivatives as well as lung edema were unchanged. If IFN-gamma and LPS were given together, pulmonary edema was less, but levels of cytokines

and

NO derivatives in serum were raised, and the mortality was greater.

IFN-gamma receptor knockout mice had more edema after LPS, but were less sensitive to the lethal effects. Treatment with anti-IL-12 antibody inhibited IFN-gamma induction and reduced mortality, but had no effect on the lung edema; exogenous IL-12 also failed to affect edema, but boosted serum cytokine levels and increased the mortality. Aminoguanidine, an inhibitor of NO synthase, protected against pulmonary edema, but did not modify the lethal effects of LPS. Clearly, in this model, early pulmonary edema and lethality are not directly related, and induced IFN-gamma has no role in causing early lung edema, but augments other events that result in death.

L27 ANSWER 14 OF 63 USPATFULL

DUPLICATE 3

AN 1999:155488 USPATFULL

TI Interleukin-12 fusion protein

IN Anderson, Robert James, London, United Kingdom

Prentice, Hugh Grant, London, United Kingdom

MacDonald, Ian Duncan, London, United Kingdom

PA Royal Free Hospital School Of Medicine, London, United Kingdom
(non-U.S.

corporation)

PI US 5994104 19991130

AI US 1996-751767 19961108 (8)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Nixon & Vanderhye, P.C.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN 13 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 3255

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to Interleukin-12 fusion proteins and nucleic acid constructs encoding them, and to the use of such fusion proteins and constructs in tumour therapy, especially therapy of leukaemia. More particularly it relates to carrying out such therapy by means of cell therapy.

L27 ANSWER 15 OF 63 USPATFULL

AN 1999:163661 USPATFULL

TI Interferon stimulating protein and uses thereof

IN Hilbert, David M., Bethesda, MD, United States

Bednarik, Daniel P., Columbia, MD, United States

Nardelli, Bernadetta, Gaithersburg, MD, United States

Murphy, Marianne, Richmond, United Kingdom

Parmelee, David, Rockville, MD, United States

Gronowski, Ann, Ballwin, MO, United States

Schreiber, Robert, St. Louis, MO, United States

PA Humn Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

Washington University, St. Louis, MO, United States (U.S. corporation)

PI US 6001806 19991214

AI US 1998-105039 19980626 (9)

PRAI US 1997-51053 19970627 (60)

DT Utility

EXNAM Primary Examiner: MacMillan, Keith D.; Assistant Examiner: Wessendorf, T. D.

LREP Hoover, Kenley K.

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 13 Drawing Figure(s); 15 Drawing Page(s)

LN.CNT 3165

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the use of the baculovirus glycoprotein, Interferon Stimulating Protein (ISP) (also known as gp67, gp64 EFP, or gp64), or the gene sequence encoding ISP, to stimulate production of **interferon**, such as for immunotherapy,

anti-viral, anti-cancer, anti-bacterial, or anti-parasitic therapy.

This

invention also relates to novel mutant forms of ISP that show enhanced biological (i.e., anti-viral) activity, increased stability, higher yield or better solubility.

L27 ANSWER 16 OF 63 USPATFULL

AN 1999:146562 USPATFULL

TI Compositions and methods for decreasing IGIF and IFN-.gamma. production by administering an ICE inhibitor

IN Su, Michael, Newton, MA, United States

Gu, Yong, Brookline, MA, United States

Livingston, David J., Newtonville, MA, United States

PA Vertex Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

PI US 5985863 19991116

AI US 1996-712878 19960912 (8)

DT Utility

EXNAM Primary Examiner: Jordan, Kimberly

LREP Fish & Neave; Haley, Jr., James F.; Dixon, Lisa A.

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 35 Drawing Page(s)

LN.CNT 1766

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and pharmaceutical compositions

for decreasing the production of **interferon-gamma** inducing factor (IGIF). The invention also relates to methods and pharmaceutical compositions for decreasing the production of **interferon-gamma** (IFN-.gamma.). The compositions comprise a therapeutically effective amount of a compound which inhibits interleukin-1.beta. converting enzyme (ICE) and a pharmaceutically acceptable carrier. The methods comprise the step of administering the above compositions to a subject. The present invention also relates to methods for treating or reducing the advancement, severity or effects of an IGIF- or

IFN-.gamma.-mediated

inflammatory, infectious or autoimmune condition.

L27 ANSWER 17 OF 63 USPATFULL

AN 1999:137002 USPATFULL

TI Growth factor inducible serine/threonine phosphatase FIN13

IN Guthridge, Mark A., New York, NY, United States

Basilico, Claudio, New York, NY, United States

PA New York University Medical Center, New York, NY, United States (U.S. corporation)

PI US 5976853 19991102

AI US 1997-822701 19970321 (8)

PRAI US 1996-13792 19960321 (60)

DT Utility

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Nashed, Nashaat T.

LREP Klauber & Jackson

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 16 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 3782

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel serine/threonine phosphatase, FIN13, which includes a collagen-homology domain, an acidic box domain, a catalytic domain, and a putative nuclear translocation sequence. The present invention

further

relates to the modulation of cellular proliferation, by regulating the activity of the novel serine/threonine phosphatase. Thus, the invention provides the phosphatase, nucleic acids encoding the phosphatase,

oligonucleotides specific for such nucleic acids, **antibodies** to the phosphatase, and methods for increasing (or decreasing) the activity of the phosphatase to inhibit (or enhance) cellular proliferation and, thus, tissue growth. Various diagnostic and therapeutic aspects of the invention particularly relate to detection and treatment of hyperproliferative disorders, neoplasms, and tumors.

In specific examples, FIN13 is expressed in proliferating cells, notably germ cells of the testes. Increased levels of expression of FIN13 in transfected cells results in a decrease in the cell growth rate.

L27 ANSWER 18 OF 63 USPATFULL

AN 1999:128718 USPATFULL

TI Lymphocyte surface receptor that binds CAML, nucleic acids encoding the same and methods of use thereof

IN Bram, Richard J., Memphis, TN, United States

Von Bulow, Gotz, Memphis, TN, United States

PA St. Jude Children's Research Hospital, Memphis, TN, United States (U.S. corporation)

PI US 5969102 19991019

AI US 1997-810572 19970303 (8)

DT Utility

EXNAM Primary Examiner: Saunders, David; Assistant Examiner: VanderVegt, F. Pierre

LREP Klauber & Jackson

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 14 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 3167

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel lymphocyte receptor protein, its DNA sequence, and its role in the calcium activation pathway is described. The protein, or genetically

engineered constructs encoding it, are shown to increase lymphocyte response, and to identify ligands of the protein receptor.

Antibodies to the proteins of the invention are generated for diagnostic therapeutics. The protein and DNA can also be used for diagnostic purposes and for identifying agents for modulating the calcium induced activation pathway. A particular advantage of the present invention is that it provides lymphocyte activation of receptor found on all B cells, but only on a subset of T cells. The receptor can thus be targeted to specifically regulate B cell responses without affecting mature T cell activity. Such targeting specificity is always advantageous, particularly where an increase or decrease of **antibody** production is desired, e.g., during an infection (increase) or to avoid immune complex deposition complications (rheumatoid arthritis, glomerulonephritis, and other auto immune conditions).

L27 ANSWER 19 OF 63 USPATFULL

AN 1999:110203 USPATFULL

TI Src-family kinase and methods of use thereof

IN Hemmati-Brivanlou, Ali, New York, NY, United States

Weinstein, Daniel C., New York, NY, United States

PA The Rockefeller University, New York, NY, United States (U.S. corporation)

PI US 5952213 19990914

AI US 1998-6675 19980113 (9)

DT Utility

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Monshipouri, Maryam

LREP Klauber & Jackson

CLMN Number of Claims: 25

ECL Exemplary Claim: 1

DRWN 15 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 2542

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a unique src-family kinase (SFK) that plays a key role in the transformation of early-stage embryonic cells to mesodermal cells. Furthermore, this src-family kinase is likely to be a proto-oncogene. The nucleic acid and amino acid sequences are disclosed.

L27 ANSWER 20 OF 63 USPATFULL

AN 1999:75759 USPATFULL

TI Low affinity human IL-12 beta2 receptor

IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5919903 19990706

AI US 1997-914520 19970819 (8)

RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996

PRAI US 1995-1701 19950801 (60)

DT Utility

EXNAM Primary Examiner: Draper, Garnette D.

LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1531

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A recombinant human IL-12 receptor complex produced on the surface of a non-human mammalian cell and free from other human proteins, the complex comprising the beta1 receptor protein complexed with a beta2 receptor protein, which complex is capable of binding to human IL-12 with high affinity. A recombinant human

IL-12 beta2 receptor protein produced on the surface of a non-human mammalian cell, free from other human proteins, in its active form. In addition, a non-human mammalian cell having expressed

on

its surface the recombinant human IL-12 beta2 receptor protein or the recombinant human IL-12 receptor complex, which cell proliferates in the presence of human IL-12. A non-human mammalian cell having the human IL-12 beta2 receptor protein or the complex expressed on its surface and which proliferates in response to human IL-12 is useful for determining whether a given compound inhibits biological activity of human IL-12 or is an IL-12 agonist.

L27 ANSWER 21 OF 63 USPATFULL

AN 1999:72711 USPATFULL

TI Altered telomere repeat binding factor 2

IN de Lange, Titia, New York, NY, United States

Steensel, Bas Van, New York, NY, United States

Bianchi, Alessandro, New York, NY, United States

PA The Rockefeller University, New York, NY, United States (U.S. corporation)

PI US 5917019 19990629

AI US 1998-18628 19980204 (9)

RLI Continuation-in-part of Ser. No. US 1997-800264, filed on 13 Feb 1997, now patented, Pat. No. US 5859183

DT Utility

EXNAM Primary Examiner: McKelvey, Terry

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN 69 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 5112

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an isolated altered vertebrate telomere repeat binding factor (A-TRFs). Also included are the corresponding nucleic acids that encode the A-TRFs of the present invention, as well as the heterodimers formed by the association of an A-TRF with a TRF.

In addition, pharmaceutical compositions containing the A-TRFs for treatment of diseases such as ataxia telangiectasia are also included. Methods of making, purifying and using the A-TRFs of the present invention are described. In addition, drug screening assays to identify drugs that mimic and/or complement the effect of the A-TRFs are presented.

L27 ANSWER 22 OF 63 USPATFULL

AN 1999:4838 USPATFULL

TI Altered telomere repeat binding factor

IN de Lange, Titia, New York, NY, United States

Steensel, Bas van, New York, NY, United States

Bianchi, Alessandro, New York, NY, United States

PA The Rockefeller University, New York, NY, United States (U.S. corporation)

PI US 5859183 19990112

AI US 1997-800264 19970213 (8)

DT Utility

EXNAM Primary Examiner: McKelvey, Terry A.

LREP Klauber & Jackson

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 29 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 3602

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an isolated altered vertebrate telomere repeat binding factor (A-TRF) that hinders the binding of a TRF to its specific telomere repeat sequence. Also included are the corresponding nucleic acids that encode the A-TRFs of the present invention, as well as the heterodimers formed by the association of an A-TRF with a TRF.

In addition, pharmaceutical compositions containing the A-TRFs for treatment of diseases such as ataxia telangiectasia are also included. Methods of making, purifying and using the A-TRFs of the present invention are described. In addition, drug screening assays to identify drugs that mimic and/or complement the effect of the A-TRFs are presented.

L27 ANSWER 23 OF 63 MEDLINE

AN 1999354937 MEDLINE

DN 99354937

TI Anti-IL-12 and anti-TNF antibodies

synergistically suppress the progression of murine collagen-induced arthritis.

AU Butler D M; Malfait A M; Maini R N; Brennan F M; Feldmann M

CS Kennedy Institute of Rheumatology, London, GB.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jul) 29 (7) 2205-12.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199910

EW 19991002

AB The co-ordinate role of the Th1 cytokine IL-12 and the proinflammatory cytokine TNF in arthritis was explored using the DBA/1 mouse model, collagen-induced arthritis (CIA). In this study, mice with established arthritis were treated with anti-IL-12 and/or anti-TNF antibodies for 10 days from the onset of disease. Clinical assessment showed that the combined antibody

treatment ameliorated disease severity to a greater extent than anti-TNF alone. Supporting these observations, histological analysis revealed that there was a reduced joint damage in the mice that received combined anti-IL-12 and anti-TNF treatment, compared to the other treatment groups. Anti-IL-12 had no statistically significant effect on the clinical outcome of disease. The combination of anti-IL-12 and anti-TNF treatment was found to reduce collagen type II (CII)-specific lymph node cell IFN-gamma production and proliferation, as well as decrease the anti-CII IgG2a:IgG1 ratio more effectively than either treatment alone. When the **antibodies** were added to synovial cells from arthritic mice and bone marrow macrophages in vitro, anti-TNF diminished IL-12 production, but anti-IL-12 had no effect on TNF production. These data suggest that, through the partial regulation of IL-12, TNF modulates the immune response in arthritis, as well as the inflammatory response. The synergistic action of anti-TNF and anti-IL-12 on CIA may provide a new therapeutic approach for treating rheumatoid arthritis.

L27 ANSWER 24 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
 AN 1999111301 EMBASE
 TI Role of gamma **interferon** in cellular immune response against murine Encephalitozoon cuniculi infection.
 AU Khan I.A.; Moretto M.
 CS I.A. Khan, Dept. of Medicine and Microbiology, HB 7506, Dartmouth Medical School, Lebanon, NH 03756, United States. Imtiaz.Khan@dartmouth.edu
 SO Infection and Immunity, (1999) 67/4 (1887-1893).
 Refs: 54
 ISSN: 0019-9567 CODEN: INFIBR
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Microsporidia are obligate intracellular protozoan parasites that cause a wide variety of opportunistic infection in patients with AIDS. Because it is able to grow in vitro, Encephalitozoon cuniculi is currently the best-studied microsporidian. T cells mediate protective immunity against this parasite. Splenocytes obtained from infected mice proliferate in vitro in response to irradiated parasites. A transient state of hyporesponsiveness to parasite antigen and mitogen was observed at day 17 postinfection.

This downregulatory response could be partially reversed by addition of nitric oxide (NO) **antagonist** to the culture. Mice infected with E. cuniculi secrete significant levels of gamma **interferon** (IFN-.gamma.). Treatment with **antibody** to IFN-.gamma. or interleukin-2 (IL-12) was able to neutralize the resistance to the parasite. Mutant animals lacking the IFN-.gamma. or IL-12 gene were highly susceptible to infection. However, mice unable to secrete NO withstood high doses of parasite challenge, similar to normal wild-type animals. These studies describe an IFN-.gamma.-mediated protection against E. cuniculi infection that is independent of NO production.

L27 ANSWER 25 OF 63 MEDLINE
 AN 1999310111 MEDLINE
 DN 99310111
 TI IL-12 directly up-regulates the expression of HLA class I, HLA class II and ICAM-1 on human melanoma cells: a mechanism for its antitumor activity?.
 AU Yue F Y; Geertsen R; Hemmi S; Burg G; Pavlovic J; Laine E; Dummer R
 CS Department of Dermatology, University of Zurich Medical School, Switzerland.
 SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jun) 29 (6) 1762-73.

JOURNAL CODE; ENS; ISSN: 0014-2980;
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199909
EW 19990902
AB IL-12 enhances cytolytic activity and proliferation of
NK and T cells, and induces cytokines such as IFN-gamma. No direct
effects

on non-hematopoietic cells have been shown. This study investigates the
effects of IL-12 on melanoma cells in vitro. We
analyzed 15 melanoma cell cultures and 1 melanoma cell line. Out of 16
samples 13 expressed the beta chain of the IL-12
receptor (IL-12Rbeta). Preincubation with IL-12
increased the surface levels of human leukocyte antigen (HLA) class I,

HLA

class II and intercellular adhesion molecule (ICAM)-1 of those cultures
with IL-12Rbeta expression. The effects of IL-12 on
HLA class I could be blocked by an IL-12-neutralizing
monoclonal **antibody** (mAb), but not by an mAb against IFN-gamma.
Melanoma cells transduced with IL-12 expressed
enhanced levels of HLA class I, HLA class II and ICAM-1 compared to
controls. Co-incubation of the melanoma cells with allogeneic peripheral
blood mononuclear cells (PBMC) resulted in enhanced proliferation and
increased production of IL-2 and IFN-gamma after pretreatment with
IL-12. IL-12 pretreatment increased
the susceptibility of melanoma cells to lysis by prestimulated autologous
PBMC. Since IL-12 induced immunocritical surface
molecules on melanoma cells, it might be beneficial during immune
interventions in melanoma patients.

L27 ANSWER 26 OF 63 MEDLINE

AN 2000005907 MEDLINE

DN 20005907

TI Enhancing Lamina propria Th1 cell responses with interleukin 12 produces
severe tissue injury [see comments].

CM Comment in: Gastroenterology 1999 Nov;117(5):1238-41

AU Monteleone G; MacDonald T T; Wathen N C; Pallone F; Pender S L

CS Department of Paediatric Gastroenterology, St. Bartholomew's and the
Royal

London School of Medicine and Dentistry, London, England.

SO GASTROENTEROLOGY, (1999 Nov) 117 (5) 1069-77.

Journal code: FH3. ISSN: 0016-5085.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 200002

EW 20000204

AB BACKGROUND & AIMS: Interleukin (IL)-12 is believed to
modulate local T-cell response in human colitis. A direct functional
relationship between IL-12 and tissue injury in human
intestine has not been reported. The aim of this study was to examine
changes that take place in explant cultures of human fetal gut after
stimulation of T cells with anti-CD3 in the presence of exogenous
IL-12/IL-18. METHODS: T cells in explants of fetal gut
were activated with anti-CD3 **antibody** and/or IL-
12 or IL-18. Mucosal pathology was determined by
immunohistochemistry. Quantitative reverse-transcription polymerase chain
reaction (RT-PCR) and enzyme-linked immunosorbent assay were used to
determine cytokine synthesis, and the production of matrix
metalloproteinases was analyzed by RT-PCR and Western blotting. RESULTS:
Activation of T cells in explants with anti-CD3 **antibody**
elicited very little **interferon** (IFN)-gamma and tumor necrosis

factor (TNF)-alpha production and no tissue injury. Addition of graded doses of IL-12 with anti-CD3 resulted in a significant increase in both IFN-gamma and TNF-alpha. This change was associated with a massive increase in stromelysin-1 expression and severe tissue injury, which was inhibitable by a stromelysin-1 inhibitor. Costimulation of explants with anti-CD3 and IL-18 induced only IFN-gamma and no tissue injury. CONCLUSIONS: IL-12 can convert a physiological T-cell signal into a strong signal with the downstream effect of elevating tissue stromelysin-1 concentration and mucosal degradation.

L27 ANSWER 27 OF 63 MEDLINE

AN 1999406560 MEDLINE

DN 99406560

TI Synergistic antitumor effects of interleukin-12 gene transfer and systemic

administration of interleukin-18 in a mouse bladder cancer model.

AU Yamanaka K; Hara I; Nagai H; Miyake H; Gohji K; Micallef M J; Kurimoto M; Arakawa S; Kamidono S

CS Department of Urology and Department of Dermatology, Kobe University School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0010, Japan.

SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1999 Sep) 48 (6) 297-302.
Journal code: CN3. ISSN: 0340-7004.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199912

EW 19991204

AB We introduced the interleukin-12 (IL-12) gene into the mouse bladder cancer cell line (MBT2) to establish sublines that secrete bioactive IL-12. IL-12-secreting MBT2 (MBT2/IL-12) sublines were completely rejected when subcutaneously implanted into immunocompetent syngeneic C3H mice. Although this antitumor effect did not change when IL-12 -secreting cells were injected into immunodeficient mice whose CD8(+) T

or

CD4(+) T cells had been depleted by the corresponding antibody, it was abrogated when natural killer cells were depleted by anti-asialoGM1

antibody. In addition, when parental MBT2 cells mixed with MBT2/IL-12 cells were subcutaneously injected into mice, admixed MBT2/IL-12 inhibited the growth of the parental tumor. Furthermore, this antitumor effect was enhanced by systemic IL-18 administration. This synergism was abrogated when the mice were treated with interferon-gamma-neutralizing antibody in vivo. In conclusion, local secretion of IL-12 led to effective antitumor activity that was enhanced by systemic administration of IL-18. Interferon-gamma plays an important role in the synergism of IL-12 gene transduction and systemic administration of IL-18.

L27 ANSWER 28 OF 63 MEDLINE

AN 1999120993 MEDLINE

DN 99120993

TI Interleukin-12 production by human alveolar macrophages is controlled by the autocrine production of interleukin-10.

AU Isler P; de Rochemonteix B G; Songeon F; Boehringer N; Nicod L P

CS Pulmonary Division, University Hospital, Geneva, Switzerland.

SO AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (1999 Feb) 20 (2) 270-8.

Journal code: AOB. ISSN: 1044-1549.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FF Briarity Journals

EM 199905

EW 19990502

AB By releasing interleukin (IL)-12 in the lung, alveolar macrophages (AM) may profoundly modify an immune response. The autocrine regulation of the heterodimeric, biologically active form of IL-12 (IL-12 p70) by IL-10 was studied, as well as the expression of its subunits of 35 kD (p35) and 40 kD (p40). AM cultured in medium alone expressed only p35 mRNA. Both p35 and p40 mRNA levels were induced by lipopolysaccharide (LPS) and were further

increased

by interferon-gamma (IFN-gamma). LPS alone induced IL-12 p40 but not IL-12 p70 production in monocytes and in AM. However, IL-12 p70 was released when the autocrine production of IL-10 was neutralized by IL-10 blocking antibody, and IL-12 p40 production increased. Although IFN-gamma markedly decreased LPS-induced IL-10 production in AM, neutralizing IL-10 further enhanced the level of LPS and

IFN-gamma-induced

IL-12 p70 in AM. In contrast, neutralizing the trace amount of IL-10 released by AM stimulated by CD40 crosslinking and IFN-gamma did not increase IL-12 p70. Thus, IL-12 p70 production by AM appears to be tightly controlled by the autocrine release of IL-10 when stimulated by LPS, or by LPS and IFN-gamma, whereas CD40 crosslinking triggered IL-12 p70 production in the absence of autocrine regulation by IL-10.

L27 ANSWER 29 OF 63 USPATFULL

AN 1998:161997 USPATFULL

TI Antibody to interleukin-12 receptor

IN Gately, Maurice Kent, Pine Brook, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

Wu, Chang-you, Belleville, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5853721 19981229

AI US 1995-381059 19950131 (8)

DT Utility

EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin

LREP Johnston, George W.; Tramaloni, Dennis P.; Kass, Alan P.

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 33 Drawing Figure(s); 22 Drawing Page(s)

LN.CNT 1418

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel antibody against the IL-12 receptor and a novel combination of antibodies against the IL-12 receptor. The novel anti-IL-12 receptor antibody, designated as 2B10, provided in accordance with the present invention binds to the human IL-12 receptor but which is not capable of inhibiting the binding of human IL-12 to the high affinity human IL-12 receptor and is not capable of neutralizing human IL-12 bioactivity by binding to human IL-12 receptor.

L27 ANSWER 30 OF 63 USPATFULL

AN 1998:160106 USPATFULL

TI Antibodies to receptors for human interleukin-12

IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States

Presky, David Howard, Glen Ridge, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5852176 19981222

AI US 1997-915495 19970820 (8)

RLI Division of Ser. No. US 1996-685118, filed on 23 Jul 1996

PRAI US 1995-1701 19950801 (60)

DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.
 CLMN Number of Claims: 1
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 1381
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB **Antibodies** to human **IL-12** beta 2 receptor protein or an **IL-12** receptor complex, the complex comprising the beta1 receptor protein complexed with a beta2 receptor protein, which complex is capable of binding to human **IL-12** with high affinity.

 L27 ANSWER 31 OF 63 USPATFULL
 AN 1998:147252 USPATFULL
 TI DNA encoding receptors for the beta-2 chain of human **IL-12**
 IN Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
 Presky, David Howard, Glen Ridge, NJ, United States
 PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
 PI US 5840530 19981124
 AI US 1996-685118 19960723 (8)
 PRAI US 1995-1701 19950801 (60)
 US 1996-18674 19960530 (60)
 DT Utility
 EXNAM Primary Examiner: Draper, Garnette D.
 LREP Johnston, George W.; Rocha-Tramaloni, Patricia S.; Silverman, Robert A.
 CLMN Number of Claims: 12
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 1424
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB A recombinant human **IL-12** beta2 receptor protein produced on the surface of a non-human mammalian cell, free from other human proteins, in its active form. In addition, a non-human mammalian cell having expressed on its surface the recombinant human **IL-12** beta2 receptor protein, which cell proliferates in the presence of human **IL-12**. A non-human mammalian cell having the human **IL-12** beta2 receptor protein on its surface and which proliferates in response to human **IL-12** is useful for determining whether a given compound inhibits biological activity of human **IL-12** or is an **IL-12** agonist.

 L27 ANSWER 32 OF 63 USPATFULL
 AN 1998:135151 USPATFULL
 TI Human receptor for interleukin-12
 IN Chua, Anne On, Wayne, NJ, United States
 Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
 PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
 PI US 5831007 19981103
 AI US 1995-419652 19950411 (8)
 RLI Division of Ser. No. US 1994-248532, filed on 31 May 1994, now patented,
 Pat. No. US 5536657 which is a continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
 DT Utility
 EXNAM Primary Examiner: Ulm, John
 LREP Johnston, George W.; Epstein, William H.; Bucholz, Briana C.
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN 35 Drawing Figure(s); 26 Drawing Page(s)
 LN.CNT 1937
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to substantially pure Interleukin-12 receptor
CDNAs and protein and uses thereof. The interleukin-12 receptor is
shown to be a member of the cytokine receptor superfamily and has a
high homology to human gp130.

L27 ANSWER 33 OF 63 USPTFLL

AN 1998:82874 USPTFLL

TI Monoclonal **antibodies** to cytotoxic lymphocyte maturation
factor

IN Gately, Maurice Kent, Montville, NJ, United States
Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
Hulmes, Jeffrey David, Ringwood, NJ, United States
Podlaski, Frank John, New City, NY, United States
Stern, Alvin Seth, Passaic Park, NJ, United States
Chizzonite, Richard Anthony, South Kent, CT, United States
Pan, Yu-Ching Eugene, Pine Brook, NJ, United States

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5780597 19980714

AI US 1995-460061 19950602 (8)

RLI Division of Ser. No. US 1994-205011, filed on 2 Mar 1994, now abandoned
which is a division of Ser. No. US 1992-857023, filed on 24 Mar 1992,
now abandoned which is a continuation-in-part of Ser. No. US
1990-572284, filed on 27 Aug 1990, now abandoned which is a
continuation-in-part of Ser. No. US 1990-520935, filed on 9 May 1990,
now abandoned which is a continuation-in-part of Ser. No. US
1989-455708, filed on 22 Dec 1989, now abandoned

DT Utility

EXNAM Primary Examiner: Cunningham, Thomas M.; Assistant Examiner: Lubet,
Martha T.

LREP Johnston, George W.; Epstein, William H.; Buchholz, Briana C.

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN 41 Drawing Figure(s); 44 Drawing Page(s)

LN.CNT 2912

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to **antibodies** which bind to a
novel cytotoxic lymphocyte maturation factor. When bound to the
cytotoxic lymphocyte maturation factor, the **antibodies** can
neutralize bioactivity of the factor.

L27 ANSWER 34 OF 63 CAPLUS COPYRIGHT 2001 ACS

AN 1998:640257 CAPLUS

DN 129:255530

TI Methods and compositions for modulating responsiveness to corticosteroids

IN Sekut, Les; Carter, Adam; Chayur, Tariq; Banerjee, Subhashis; Tracey,
Daniel E.

PA Basf A.-G., Germany

SO PCT Int. Appl., 112 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9841232	A2	19980924	WO 1998-US4916	19980312
	WO 9841232	A3	20001005		

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,
ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,

US

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
GA, GN, ML, MR, NE, SN, TD, TG

AU 9867604 A1 19981012 AU 1998-67604 19970318
 EP 988700 A1 20000510 EP 1998-912929 19980312
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
 BR 9810409 A 20000822 BR 1998-10409 19980312
 NO 9904506 A 19991117 NO 1999-4506 19990917
 PRAI US 1997-820692 19970318
 US 1998-16346 19980130
 WO 1998-US4916 19980312
 AB Method for modulating responsiveness to corticosteroids in a subject are provided. In the method of the invention, an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in the subject is administered to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when the corticosteroid is given alone. The method can be used to, for example, reverse steroid resistance of to increase steroid sensitivity, or to ameliorate the steroid rebound effect when subjects are taken off corticosteroid treatment. In one embodiment, the agent is an IL-18 **antagonist**. In another embodiment, the agent is an interleukin-12 (IL-12) **antagonist**. In yet another embodiment, the agent is an NK cell **antagonist**. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-IL-12 monoclonal **antibody**. In yet another preferred embodiment, the agent is an anti-asialo-GM1 **antibody** or an NK1.1 **antibody**. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunol. diseases and disorders. Pharmaceutical compns. comprising an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred compn. comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L27 ANSWER 35 OF 63 MEDLINE
 AN 1999030651 MEDLINE
 DN 99030651
 TI Inhibition of **interferon** gamma induced interleukin 12 production: a potential mechanism for the anti-inflammatory activities of tumor necrosis factor.
 AU Hodge-Dufour J; Marino M W; Horton M R; Jungbluth A; Burdick M D; Strieter R M; Noble P W; Hunter C A; Pure E
 CS Immunology Graduate Group, University of Pennsylvania, Philadelphia, PA 19104, USA.
 NC HL50057 (NHLBI)
 HL60539 (NHLBI)
 AI42334 (NIAID)
 +
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Nov 10) 95 (23) 13806-11.
 Journal code: PV3. ISSN: 0027-8424.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199902
 EW 19990204
 AB Inflammation is associated with production of cytokines and chemokines

that recruit and activate inflammatory cells. Interleukin (IL) 12 produced by macrophages in response to various stimuli is a potent inducer of interferon (IFN) gamma production. IFN-gamma, in turn, markedly enhances IL-12 production. Although the immune response is typically self-limiting, the mechanisms involved are unclear. We demonstrate that IFN-gamma inhibits production of chemokines (macrophage inflammatory proteins MIP-1alpha and MIP-1beta). Furthermore, pre-exposure to tumor necrosis factor (TNF) inhibited IFN-gamma priming for production of high levels of IL-12 by macrophages in vitro. Inhibition of IL-12 by TNF can be mediated by both IL-10-dependent and IL-10-independent mechanisms. To determine whether TNF inhibition of IFN-gamma-induced IL-12 production contributed to the resolution of an inflammatory response in vivo, the response of TNF+/+ and TNF-/- mice injected with *Corynebacterium parvum* were compared. TNF-/- mice developed a delayed, but vigorous, inflammatory response leading to death, whereas TNF+/+ mice exhibited a prompt response that resolved. Serum IL-12 levels were elevated 3-fold in *C. parvum*-treated TNF-/- mice compared with TNF+/+ mice. Treatment with a neutralizing anti-IL-12 antibody led to resolution of the response to *C. parvum* in TNF-/- mice. We conclude that the role of TNF in limiting the extent and duration of inflammatory responses in vivo involves its capacity to regulate macrophage IL-12 production. IFN-gamma inhibition of chemokine production and inhibition of IFN-gamma-induced IL-12 production by TNF provide potential mechanisms by which these cytokines can exert anti-inflammatory/repair function(s).

L27 ANSWER 36 OF 63 MEDLINE

AN 1998143355 MEDLINE

DN 98143355

TI Therapeutic effect of interleukin 12 on mouse haemangiosarcomas is not associated with an increased anti-tumour cytotoxic T-lymphocyte activity.

AU Vizler C; Rosato A; Calderazzo F; Quintieri L; Fruscella P; Wainstok de Calmanovici R; Mantovani A; Vecchi A; Zanolello P; Collavo D

CS Department of Oncology and Surgical Sciences, University of Padua, Italy.

SO BRITISH JOURNAL OF CANCER, (1998 Feb) 77 (4) 656-62.
Journal code: AV4. ISSN: 0007-0920.

CY SCOTLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199805

EW 19980501

AB In syngeneic mice, the H5V polyoma middle-T oncogene-transformed endothelioma cell line induces Kaposi's sarcoma-like cavernous haemangiomas that regress transiently, probably because of an anti-tumour immune response, but eventually grow progressively and kill the host. To evaluate the generation of tumour-specific cytotoxic T lymphocytes (CTLs),

spleen cells of tumour-bearing mice were restimulated with irradiated H5V cells in mixed leucocyte-tumour cell cultures. Tumour-specific CTLs were demonstrable only when low numbers of H5V stimulator cells were used (<1 H5V cell per 50 splenocytes). We found that H5V cells secrete immunosuppressive mediators because CTL generation was blocked when H5V cells culture supernatants were added to allogeneic mixed leucocyte cultures. As numerous tumour-derived immunosuppressive mediators may interfere with interleukin 12 (IL-12) production, we tested whether IL-12 treatment of the tumour-bearing mice would augment their immune response and thus suppress tumour growth. Indeed, IL-12 inhibited tumour growth and prevented

NR

in vivo. Moreover, the anti-tumour activity in IL-12-treated mice was abrogated by anti-interferon (IFN)-gamma monoclonal antibody (MAb) co-administration. These results strongly suggest that the anti-tumour effect of IL-12 is principally mediated by IFN-gamma release that in turn blocks H5V cell proliferation and induces the release of factors that suppress angiogenesis.

L27 ANSWER 37 OF 63 MEDLINE

AN 1999012298 MEDLINE

DN 99012298

TI Analysis of Mycobacterium tuberculosis-derived substance which induces interleukin-12 production from macrophages.

AU Higuchi K; Harada N; Uchiyama T; Fujiwara H; Ueda C; Tsuyuguchi I; Nakamura R M; Kobayashi K; Aoki M

CS Department of Basic Research, Japan Anti-Tuberculosis Association, Tokyo, Japan.

SO KEKKAKU, (1998 Sep) 73 (9) 531-43.

Journal code: KUO. ISSN: 0022-9776.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese

EM 199904

EW 19990402

AB Protection of hosts against tuberculosis depends on expression of cellular

immunity. To express cellular immunity, interleukin 12 (IL-12) has been shown to play an important role. Although Mycobacterium tuberculosis is known to induce IL-12 from macrophages (M phi s), the mechanism for the induction is still unclear. To understand the mechanisms of IL-12 induction from M phi s by M. tuberculosis, the IL -12-inducing ability of substances derived from M. tuberculosis was investigated in vitro. Production of IL-12 in culture medium of M phi s was measured by ELISA system using specific antibodies. Live M. tuberculosis H37Rv induced slightly higher IL-12 production than live M. tuberculosis H37Ra upon stimulation of human or mouse alveolar macrophages (hAM phi s or mAM phi s). Heat-killed M. tuberculosis failed to induce IL-12 production of alveolar macrophages (AM phi). The responses of hAM phi s and mAM phi s to M. tuberculosis were remarkably different. mAM phi s produced five times larger amount of IL-12, compared with that from hAM phi s. Human peripheral blood mononuclear cells (PBMC) obtained by the density gradient centrifugation were also used for induction of IL-12 production. Although production levels of IL-12 from PBMC stimulated with M. tuberculosis were below the detectable level, addition of interferon-gamma (IFN-gamma) or neutralizing antibody against IL-10 augmented the production of IL-12 from PBMC, suggesting that IFN-gamma and IL-10 regulate the production of IL-12 from M phi positively and negatively, respectively. To characterize the physicochemical properties of IL -12-inducing molecules, M. tuberculosis H37Rv was disrupted by pressing with 1,000 bar and centrifuged and separated into cytosol and cell wall fraction. The culture filtrate was also examined on IL -12-inducing activity. Among the three subjects examined, cytosol was found to induce the highest production of IL-12 from mAM phi s 1 day after the stimulation. Addition of IFN-gamma to the cytosol fraction markedly increased the production of IL-12 from mAM phi s. The molecular weight of IL -12-inducing substance was shown to be more than 30kDa by fractionating with molecular filters. Treatment of 30kDa-fraction with IL-12-inducing activity by proteinase K completely

abolished the activity. Furthermore, approximately 90% of IL-12-inducing activity of 30kDa-fraction was lost by proteinase K treatment even in the presence of IFN-gamma. These results indicate that the major component of IL-12-inducing activity is a protein. The identification of this IL-12-inducing active substance may provide a new therapeutic tool for tuberculosis.

- L27 ANSWER 38 OF 63 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
AN 1998110845 EMBASE
TI Interleukin 12 upregulates the release of vascular permeability factor by peripheral blood mononuclear cells from patients with lipoid nephrosis.
AU Matsumoto K.; Ohi H.; Kanmatsuse K.
CS Dr. K. Matsumoto, 2nd Department of Internal Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kami-Machi, Itabashi-ku, Tokyo 173, Japan
SO Nephron, (1998) 78/4 (403-409).
Refs: 16
ISSN: 0028-2766 CODEN: NPRNAY
CY Switzerland
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LA English
SL English
AB The vascular permeability factor (VPF) is a lymphokine that has been shown to play a role in lipoid nephrosis (LN). Prior studies have shown that interleukin (IL) 12 promotes T helper type 1 differentiation and enhances production of T helper type 1 cytokines such as gamma interferon and IL-2. We, therefore, investigated the effects of recombinant human IL-12 on the release of VPF by peripheral blood mononuclear cells (PBMC) from LN patients. The VPF activity was measured according to the method of Ovary, with minor modifications. The goal of the present study was to examine the importance of IL-12 in concanavalin A induced VPF release in vitro. The levels of VPF were measured in a group of healthy subjects, LN patients with or without the nephrotic syndrome, and patients suffering from IgA nephropathy. There was a significantly increased concanavalin A induced release of VPF in LN and IgA nephropathy patients with nephrotic syndrome as compared with normal controls. Recombinant human IL-12 was found to enhance VPF release in a dose-dependent manner. Neutralization of endogenously produced IL-12 by anti-IL-12 antibody resulted in a decreased release of VPF by LN PBMC. These data indicate that endogenously produced IL-12 functions as a costimulatory molecule in vitro. Our data show that IL-12 can upregulate the release of VPF derived from LN PBMC. Thus IL-12 might be a potent adjuvant for inducing VPF. Therefore, IL-12 antagonists may interfere with newly initiated and ongoing VPF release associated with nephrotic syndrome.
- L27 ANSWER 39 OF 63 MEDLINE
AN 1998145812 MEDLINE
DN 98145812
TI Blockade of IL-12 during the induction of collagen-induced arthritis (CIA) markedly attenuates the severity of the arthritis.
AU Malfait A M; Butler D M; Presky D H; Maini R N; Brennan F M; Feldmann M
CS Kennedy Institute of Rheumatology, London, UK.
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1998 Feb) 111 (2) 377-83.
Journal code: DD7. ISSN: 0009-9104.
CY ENGLAND: United Kingdom